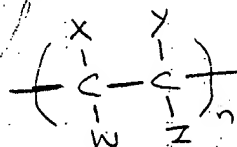


102457
SEARCH REQUEST FORMRequestor's Name: Ganapathy Krishnan Serial Number: 09 1937991Date: 8/26/03 Phone: 305-4837 Art Unit: 1623
off: 8208 MR: 8319**Search Topic:**

Please write a detailed statement of search topic: Describe specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples or relevant citations, authors, keywords, etc., if known. For sequences, please attach a copy of the sequence. You may include a copy of the broadest and/or most relevant claim(s).

Search for:
A polymer having the structure:



wherein X, Y, Z is any substituent including hydrogen.
W is a carbohydrate chain. The carbohydrate chains are listed in claim 3.

L1

8/29 **STAFF USE ONLY**Date completed: 8/29Searcher: HandyTerminal time: 45Elapsed time: 60CPU time: Total time: Number of Searches: Number of Databases: **Search Site** STIC CM-1 Pre-S**Type of Search** N.A. Sequence A.A. Sequence StructureX Bibliographic**Vendors** IG\$450 STN Dialog APS Geninfo SDC DARC/Questel Other



STIC SEARCH RESULTS FEEDBACK FORM

Biotech-Chem Library

Questions about the scope or the results of the search? Contact *the searcher or contact*:

Mary Hale, Information Branch Supervisor
308-4258, CM1-1E01

Voluntary Results Feedback Form

➤ I am an examiner in Workgroup: Example: 1610

➤ Relevant prior art **found**, search results used as follows:

- ☐ 102 rejection
- ☐ 103 rejection
- ☐ Cited as being of interest.
- ☐ Helped examiner better understand the invention.
- ☐ Helped examiner better understand the state of the art in their technology.

Types of relevant prior art found:

- ☐ Foreign Patent(s)
- ☐ Non-Patent Literature
(journal articles, conference proceedings, new product announcements etc.)

➤ Relevant prior art **not found**:

- ☐ Results verified the lack of relevant prior art (helped determine patentability).
- ☐ Results were not useful in determining patentability or understanding the invention.

Comments:

Drop off or send completed forms to STIC/Biotech-Chem Library CM1 - Circ. Desk



A \Rightarrow carbohydrate polymer
will be indexed by
its monomers

CT = controlled terms
PFT = old, new, "used
for" terms
NT = narrower
term

\Rightarrow d que 141 text approach

L31	59141	SEA FILE=HCAPLUS ABB=ON	PLU=ON	MUCOPOLYSACCHARIDES+PFT,NT/CT
L32	358592	SEA FILE=HCAPLUS ABB=ON	PLU=ON	VINYL COMPOUNDS+PFT,NT/CT
L33	33892	SEA FILE=HCAPLUS ABB=ON	PLU=ON	(HEPARIN OR HEPARAN OR DERMATAN OR CHONDROITIN)/OBI
L34	2312	SEA FILE=HCAPLUS ABB=ON	PLU=ON	L31 AND L32
L35	776	SEA FILE=HCAPLUS ABB=ON	PLU=ON	L34 AND L33
L36	135	SEA FILE=HCAPLUS ABB=ON	PLU=ON	L33(L)VINYL
L37	94	SEA FILE=HCAPLUS ABB=ON	PLU=ON	L36 AND L35
L38	92	SEA FILE=HCAPLUS ABB=ON	PLU=ON	L37 AND PY<2003
L39	23	SEA FILE=HCAPLUS ABB=ON	PLU=ON	L38 AND (ETHYLEN? OR ETHENYL? OR STYREN?)/OBI
L40	22	SEA FILE=HCAPLUS ABB=ON	PLU=ON	L38 AND (POLYETHYLEN? OR POLYETHENYL? OR POLYSTYREN?)/OBI
L41	39	SEA FILE=HCAPLUS ABB=ON	PLU=ON	(L39 OR L40) 39 cites

\rightarrow includes the
subheading
glycosaminoglycans
1/2 heparin, dermatan
1/2 chondroitin
derivatives

\Rightarrow d que 145 Registry approach

L10	159958	SEA FILE=REGISTRY ABB=ON	PLU=ON	PVIN/PCT \leftarrow poly vinyl polymer
L11	106205	SEA FILE=REGISTRY ABB=ON	PLU=ON	PSTY/PCT \leftarrow poly styren " "
L15	22253	SEA FILE=REGISTRY ABB=ON	PLU=ON	7664-93-9/CRN sulfate as a polymer component
L17	1195	SEA FILE=REGISTRY ABB=ON	PLU=ON	L15 AND OC5/ES \leftarrow ring
L18	600	SEA FILE=REGISTRY ABB=ON	PLU=ON	L17 AND ("GLUCOPYRANOSIDE" OR "GLUCOPYRANOSYL")
L20	1	SEA FILE=REGISTRY ABB=ON	PLU=ON	L18 AND (L10 OR L11)
L21	19	SEA FILE=REGISTRY ABB=ON	PLU=ON	(L10 OR L11) AND ("DERMATAN" OR "HEPARIN" OR "HEPERAN" OR "CHONDROITIN")
L22	536807	SEA FILE=REGISTRY ABB=ON	PLU=ON	"ETHENYL"
L23	11	SEA FILE=REGISTRY ABB=ON	PLU=ON	L22 AND ("DERMATAN" OR "HEPARIN" OR "HEPERAN" OR "CHONDROIN")
L24	11	SEA FILE=REGISTRY ABB=ON	PLU=ON	L23 AND PMS/CI \leftarrow polymer
L25	20	SEA FILE=REGISTRY ABB=ON	PLU=ON	L24 OR L21
L43	1	SEA FILE=HCAPLUS ABB=ON	PLU=ON	L20
L44	15	SEA FILE=HCAPLUS ABB=ON	PLU=ON	L25
L45	16	SEA FILE=HCAPLUS ABB=ON	PLU=ON	(L43 OR L44) AND PY<2003 16 cites

\Rightarrow s 141 or 145

L47 55 L41 OR L45

\Rightarrow d ibib abs hitstr 1-55

L47 ANSWER 1 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2002:793739 HCAPLUS

DOCUMENT NUMBER: 137:284439

TITLE: Glycosaminoglycan functional polymer and adhesion
protein complexes and applications thereof

\nearrow
p1-2 were not given
they were junked

INVENTOR(S): Yura, Hirofumi; Ishihara, Masayuki; Saito, Yoshio;
 Ono, Katsuaki; Sato, Masato
 PATENT ASSIGNEE(S): Netech Inc., Japan
 SOURCE: PCT Int. Appl., 34 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002081619	A1	20021017	WO 2002-JP3287	20020402 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: JP 2001-102883 A 20010402

AB It is intended to construct environment similar to an extracellular matrix by combining a glycosaminoglycan (GAG) functional polymer with a cell adhesion protein such as collagen, and the GAG functional polymer/protein complexes characterized in that the GAG functional polymer, which has a sugar chain contg. a structure corresponding to at least a part of the basic skeleton of GAG introduced into the main chain of a vinyl-type polymer, is carried on a cell adhesive protein; differentiation and proliferation of cells can be controlled in the novel material and the complexes can be used as cell culture materials and tissue regeneration materials. Heparin-carrying polystyrene (HCPS) was prepd. The HCPS efficiently bound to collagen-coated cell culture plate, thereby retaining the binding of vascular endothelial growth factor (VEGF)₁₆₅ or fibroblast growth factor (FGF)-2. Human umbilical vein endothelial cells showed a good adherence to the HCPS-bound collagen substrate.

IT 9005-49-6DP, Heparin, reaction products with polystyrene 25322-46-7DP, Chondroitin sulfate C, reaction products with polystyrene
 RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (glycosaminoglycan-carrying vinyl polymers binding with proteins for cell adhesion)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 25322-46-7 HCAPLUS

CN Chondroitin, 6-(hydrogen sulfate) (9CI) (CA INDEX NAME)

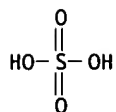
CM 1

CRN 9007-27-6
 CMF Unspecified
 CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 7664-93-9
 CMF H2 O4 S



IT 24967-94-0D, Dermatan sulfate, reaction products with
 vinyl polymers
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (glycosaminoglycan-carrying vinyl polymers binding with
 proteins for cell adhesion)
 RN 24967-94-0 HCAPLUS
 CN Dermatan, hydrogen sulfate (ester) (9CI) (CA INDEX NAME)

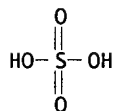
CM 1

CRN 75634-40-1
 CMF Unspecified
 CCI MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 7664-93-9
 CMF H2 O4 S



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 2 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 2002:332077 HCAPLUS
 DOCUMENT NUMBER: 136:345860
 TITLE: Preparation of hydrophobic multicomponent
 heparin conjugates for antithrombogenic
 coatings
 INVENTOR(S): Byun, Young Ro; Moon, Hyun Tae
 PATENT ASSIGNEE(S): Mediplex Corp., S. Korea
 SOURCE: PCT Int. Appl., 47 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002034312	A1	20020502	WO 2000-KR1255	20001103 <--
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			

AU 2001011769 A5 20020506 AU 2001-11769 20001103 <--
 EP 1333871 A1 20030813 EP 2000-973237 20001103

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO, MK, CY, AL

PRIORITY APPLN. INFO.: KR 2000-62668 A 20001024
 WO 2000-KR1255 W 20001103

AB The present invention provides hydrophobic heparin conjugates which are sol. not in water but in org. solvents, a prepg. method and a use thereof. Particularly, the present invention provides the hydrophobic heparin conjugates which are prepd. by covalently binding polymer and hydrophobic materials to heparin. The hydrophobic heparin conjugates of the present invention maintain a good antithrombogenic effect and are insol. in water by their hydrophobicity, so they can be effectively used for coating agents to modify the surface of medical devices. For example, a hydrophobic multicomponent heparin conjugates were synthesized from heparin, polyacrylic acid and octadecylamine in a molar ratio of 1:5:100. The surface of angiocatheter made of polyurethane and glass were coated with the conjugate by a dipping method and dried. The heparin/polyacrylic acid/octadecylamine conjugate showed great adhesiveness to the materials and had no peeling phenomena by swelling in aq. soln. The hydrophobic multicomponent heparin conjugates were adhered to the material with stability while maintaining the unique characteristics of heparin and antithrombotic activity.

IT 9002-89-5DP, Polyvinyl alcohol, conjugates with heparin

9004-61-9DP, Hyaluronic acid, conjugates with heparin

9005-49-6DP, Heparin, conjugates with macromols.

9012-76-4DP, Chitosan, conjugates with heparin

RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use);

BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of hydrophobic multicomponent heparin conjugates for antithrombogenic coatings for prosthetics and medical goods)

RN 9002-89-5 HCAPLUS

CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5

CMF C2 H4 O

H₂C=CH-OH

RN 9004-61-9 HCAPLUS

CN Hyaluronic acid (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 9012-76-4 HCAPLUS

CN Chitosan (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 3 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2001:713823 HCAPLUS

DOCUMENT NUMBER: 135:262268

TITLE: Pharmaceutical dosage form for oral administration of hydrophilic drugs, particularly low molecular weight heparin

INVENTOR(S): Chen, Feng-Jing; Patel, Mahesh V.; Fikstad, David T.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 21 pp., Cont.-in-part of U.S. Ser. No. 375,636.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 8
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2001024658	A1	20010927	US 2000-751968	20001229 <--
US 6458383	B2	20021001		
US 6309663	B1	20011030	US 1999-375636	19990817 <--
WO 2001012155	A1	20010222	WO 2000-US18807	20000710 <--
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
US 2002032171	A1	20020314	US 2001-877541	20010608 <--
WO 2002053100	A2	20020711	WO 2001-US50752	20011228 <--
WO 2002053100	A3	20030327		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
PRIORITY APPLN. INFO.:			US 1999-375636	A2 19990817
			WO 2000-US18807	A 20000710
			US 1999-345615	A2 19990630
			US 2000-751968	A2 20001229

AB A delayed release pharmaceutical dosage form for oral administration of a hydrophilic drug, e.g., a polysaccharide drug such as low mol. wt. heparin, are provided. The dosage form comprises a compn. of: (a) a therapeutically effective amt. of low mol. wt. heparin; (b) a bile salt or bile acid; (c) at least one surfactant selected from hydrophilic surfactants, lipophilic surfactants, and mixts. thereof; and a means for delaying release of the compn. from the dosage form following oral administration. Osmotic drug delivery systems for oral administration of a hydrophilic drug are also provided, wherein an osmotically activated device houses the drug, a bile salt or bile acid, and at least one surfactant selected from the group consisting of hydrophilic surfactants, lipophilic surfactants, and mixts. thereof. Methods for administering hydrophilic drugs, particularly polysaccharide drugs such as low mol. wt. heparin, are also provided. Capsules contg. Enoxaparin sodium (a LMW heparin) 50, deoxycholic acid sodium salt 100, Incrocas 35 300, and Capryol 90 300 mg were prepd. The capsules were dipped briefly in a soln. of cellulose acetate phthalate 11, triacetin 2.2% in acetone and dried in air at room temp. The capsule were dipped and dried repeatedly until a coating wt. of .1 to req. 10% (disoln. pH range of about 5.5-6.5 was achieved).

IT 9003-20-7, Polyvinyl acetate 9003-39-8, Polyvinyl pyrrolidone 9004-61-9, Hyaluronic acid 9005-49-6, Heparin, biological studies 9041-08-1, Enoxaparin sodium 24937-78-8, Ethylene-vinyl acetate copolymer 25609-89-6, Vinylacetate crotonic acid copolymer

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (pharmaceutical dosage form for oral administration of hydrophilic

drugs, particularly low mol. wt. heparin)

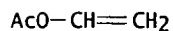
RN 9003-20-7 HCAPLUS

CN Acetic acid ethenyl ester, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 108-05-4

CMF C4 H6 O2



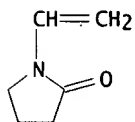
RN 9003-39-8 HCAPLUS

CN 2-Pyrrolidinone, 1-ethenyl-, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 88-12-0

CMF C6 H9 N O



RN 9004-61-9 HCAPLUS

CN Hyaluronic acid (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 9041-08-1 HCAPLUS

CN Heparin, sodium salt (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

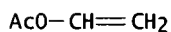
RN 24937-78-8 HCAPLUS

CN Acetic acid ethenyl ester, polymer with ethene (9CI) (CA INDEX NAME)

CM 1

CRN 108-05-4

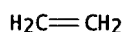
CMF C4 H6 O2



CM 2

CRN 74-85-1

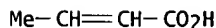
CMF C2 H4



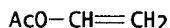
RN 25609-89-6 HCAPLUS

CN 2-Butenoic acid, polymer with ethenyl acetate (9CI) (CA INDEX NAME)

CM 1

CRN 3724-65-0
CMF C4 H6 O2

CM 2

CRN 108-05-4
CMF C4 H6 O2

L47 ANSWER 4 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2000:460978 HCAPLUS

DOCUMENT NUMBER: 133:355165

TITLE: Polymeric systems based on derivatives of
ethylene-vinyl alcohol copolymers

AUTHOR(S): Marconi, W.; Cordelli, S.; Napoli, A.; Piozzi, A.

CORPORATE SOURCE: Department of Chemistry, University of Rome "La
Sapienza", Rome, 00185, Italy

SOURCE: Journal of Bioactive and Compatible Polymers (2000), 15(3), 257-271

CODEN: JBCPEV; ISSN: 0883-9115

PUBLISHER: Technomic Publishing Co., Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB To obtain polymers with improved hemocompatibility properties, com. ethylene-vinyl alc. copolymers (EVAL) were chem. modified, by the introduction of stearyl groups to bind albumin and quaternary ammonium groups to bind heparin. These novel polymer composites were characterized by FT-IR and 1H-NMR spectroscopy. The amt. of heparin and albumin bonded by these polymers were detd. and the influence of the adsorption sequence (heparin-albumin or vice versa) was evaluated. The amt. of adsorbed albumin was proportional to the stearyl content of the polymer. When heparin was exposed to polymer surfaces contg. quaternary ammonium groups, the amt. of bonded heparin was proportional to the content of pos. charged groups. An in vitro evaluation of the anti-clotting properties and of the adhesion characteristics of the polymer surfaces contg. both stearyl groups and quaternary ammonium groups exhibited, after heparinization, good anticoagulant activity. This activity was retained after the albuminization. Platelet adhesion tests showed that albuminization of polymer films contg. only stearyl residues improved their behavior towards platelet adhesion.

IT 9005-49-6DP, Heparin, reaction products with activated EVAL, biological studies 25067-34-9DP, Eval, heparinized or albuminized

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(biocompatible polymeric systems based on derivs. of ethylene -vinyl alc. copolymers)

RN 9005-49-6 HCAPLUS

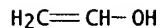
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 25067-34-9 HCAPLUS

CN Ethenol, polymer with ethene (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5
CMF C2 H4 O

CM 2

CRN 74-85-1
CMF C2 H4

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 5 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2000:182122 HCAPLUS

DOCUMENT NUMBER: 133:22375

TITLE: Multi-layered thromboresistant thin films on
poly(vinylchloride) (PVC) surfaces; a spectroscopic
study

AUTHOR(S): Kim, Huang; Urban, Marek W.

CORPORATE SOURCE: School of Polymers and High Performance Materials, The
University of Southern Mississippi, Hattiesburg, MS,
39406, USA

SOURCE: Polymeric Materials Science and Engineering (

2000), 82, 392-393

CODEN: PMSEGD; ISSN: 0743-0515

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The formation of multi-layered structures that consist of
polyethyleneimine, dextran sulfate and heparin sulfate attached to PVC
surfaces is reported. ATR FT-IR spectra of the polymers were detd.

IT 272442-93-0P

RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use);

BIOL (Biological study); PREP (Preparation); USES (Uses)

(spectroscopic study of multi-layered thromboresistant thin films on
PVC surfaces)

RN 272442-93-0 HCAPLUS

CN Heparin, compd. with aziridine graft polymer with chloroethene (9CI) (CA
INDEX NAME)

CM 1

CRN 9005-49-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 272442-92-9
CMF (C2 H5 N . C2 H3 Cl)x
CCI PMS

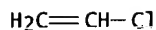
CM 3

CRN 151-56-4
CMF C2 H5 N



CM 4

CRN 75-01-4
CMF C2 H3 C1



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 6 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2000:144524 HCAPLUS

DOCUMENT NUMBER: 132:185484

TITLE: Thromboresistant coating of medical devices using silanes or siloxanes

INVENTOR(S): Shah, Chirag B.; Tedeschi, Gene; Wolfgang, Laurel L.

PATENT ASSIGNEE(S): Medtronic Ave, Inc., USA

SOURCE: Eur. Pat. Appl., 24 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 982041	A1	20000301	EP 1999-116428	19990820 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2001034336	A1	20011025	US 2001-862710	20010523 <--

PRIORITY APPLN. INFO.: US 1998-138464 A 19980821

AB Coatings are provided in which biopolymers may be covalently linked to a substrate. Such biopolymers include those that impart thromboresistance and/or biocompatibility to the substrate, which may be a medical device. Coatings disclosed include those that permit coating of a medical device in a single layer, including coatings that permit applying the single layer without a primer. Suitable biopolymers include heparin complexes, and linkage may be provided by a silane having isocyanate functionality. Plasma deposition and solvent swelling techniques are described as preferred methods of depositing a derivatized silane or a silane-heparin coating. Stainless steel stents were coated with a formulation of 1% heparin-tridodecylmethylammonium chloride complex, 2% silane and 97% THF. The stents were dipped once in the formulation, with a dwell time of 5 s at a coating speed of 10 in/min to give a single layer of coating. The coating showed heparin activity after 1 wk of exposure to saline.

IT 259665-61-7

RL: DEV (Device component use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(thromboresistant coating of medical devices using silanes or siloxanes)

RN 259665-61-7 HCAPLUS

CN Heparin, compd. with 1-ethenyl-2-pyrrolidinone homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 9005-49-6
 CMF Unspecified
 CCI PMS, MAN

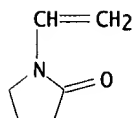
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 9003-39-8
 CMF (C6 H9 N O)x
 CCI PMS

CM 3

CRN 88-12-0
 CMF C6 H9 N O



L47 ANSWER 7 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2000:98671. HCAPLUS

DOCUMENT NUMBER: 132:156879

TITLE: Physiologically compatible ion complex, coating material for medical goods and coating method using it

INVENTOR(S): Yoshioka, Hiroshi; Mori, Yuichi; Kubota, Sunao

PATENT ASSIGNEE(S): M & M Laboratory Co., Ltd., Japan; Terumo Kabushiki Kaisha

SOURCE: PCT Int. Appl., 43 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000006651	A1	20000210	WO 1999-JP4021	19990727 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9949283	A1	20000221	AU 1999-49283	19990727 <--
EP 1020495	A1	20000719	EP 1999-933116	19990727 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 6555225	B1	20030429	US 2000-535532	20000327
PRIORITY APPLN. INFO.: JP 1998-211008 A 19980727				
WO 1999-JP4021 W 19990727				

AB The ion complex is insol. in water and sol. in water-contg. org. solvents and comprises a water-insol. polyion and a water-sol. polyion preferably from physiol. active compd. having blood anticoagulant (e.g., heparin) or

antibacterial activity. The ion complex is useful as coating for use on medical goods, e.g., surgical tubes, for reducing health complication. Thus, dissolving diacetone acrylamide 2.0, Blemmer PME 4000 (PEG monomethacrylate) 0.14, a 75% aq. soln. of N,N-dimethylaminopropylacrylamide Me chloride quaternary ammonium salt 0.19 and Na heparin 0.14 g in water 7.5 g, mixing with 6 g EtOH, 0.2 mL a 10% ammonium persulfate aq. soln. and 20 .mu.L N,N,N',N'-tetramethylethylenediamine at room temp. for 2 h, evapg., washing and freeze drying gave an ion complex which was insol. in water and sol. in aq. EtOH. A viscous coating was obtained by mixing 0.2 g the complex in 2.3 g an aq. EtOH (18% water content).

IT 257877-23-9P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); IMF (Industrial manufacture); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(physiol. compatible ion complex, coating material for medical goods and coating method)

RN 257877-23-9 HCAPLUS

CN D-Streptamine, 0-3-amino-3-deoxy-.alpha.-D-glucopyranosyl-(1.fwdarw.6)-O-[2,6-diamino-2,3,4,6-tetradeoxy-.alpha.-D-erythro-hexopyranosyl-(1.fwdarw.4)]-2-deoxy-, sulfate (salt), compd. with N-(1,1-dimethyl-3-oxobutyl)-2-propenamide polymer with ethyl 2-propenoate and sodium ethenylbenzenesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 257877-22-8

CMF (C9 H15 N O2 . C8 H8 O3 S . C5 H8 O2 . Na)x

CCI PMS

CM 2

CRN 27457-28-9

CMF C8 H8 O3 S . Na

CCI IDS

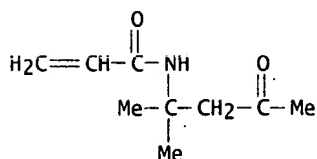
D1- CH=CH₂D1- SO₃H

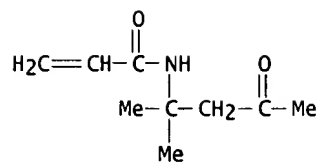
● Na

CM 3

CRN 2873-97-4

CMF C9 H15 N O2

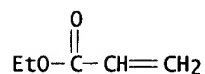




CM 4

CRN 140-88-5

CMF C5 H8 O2



CM 5

CRN 58580-55-5

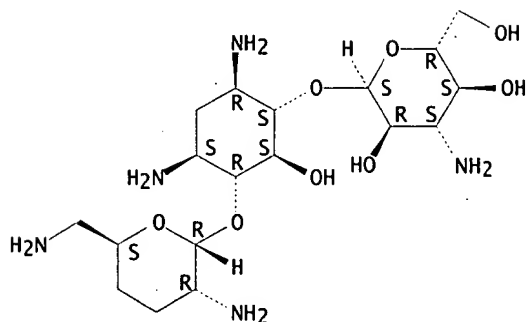
CMF C18 H37 N5 O8 . x H2 O4 S

CM 6

CRN 34493-98-6

CMF C18 H37 N5 O8

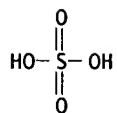
Absolute stereochemistry.



CM 7

CRN 7664-93-9

CMF H2 O4 S .



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 8 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1999:764076 HCAPLUS
 DOCUMENT NUMBER: 132:26813
 TITLE: Preparation and anticoagulant activity of amphiphilic heparin conjugates
 INVENTOR(S): Byun, Youngro; Lee, Yong Kyu
 PATENT ASSIGNEE(S): Mediplex Corporation, Korea, S. Korea
 SOURCE: PCT Int. Appl., 32 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9961481	A1	19991202	WO 1999-KR242	19990514 <--
W: AE, AT, AU, BR, CA, CH, CN, DE, DK, ES, FI, GB, HU, ID, IN, JP, KP, KZ, MN, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, TR, UA, ZA				
US 6245753	B1	20010612	US 1999-300173	19990427 <--
AU 9937358	A1	19991213	AU 1999-37358	19990514 <--
GB 2342357	A1	20000412	GB 1917-94	19990514 <--
DE 19981169	T	20001116	DE 1999-19981169	19990514 <--
GB 2342357	B2	20020327	GB 2000-1794	19990514 <--
JP 2002516355	T2	20020604	JP 2000-550884	19990514 <--
US 2002013292	A1	20020131	US 2001-852131	20010509 <--
US 6589943	B2	20030708		
WO 2002089820	A1	20021114	WO 2001-KR1722	20011012 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRIORITY APPLN. INFO.:			KR 1998-19469	A 19980528
			KR 1999-14003	A 19990420
			US 1999-300173	A 19990427
			WO 1999-KR242	W 19990514
			US 2001-852131	A 20010509

AB Amphiphilic heparin derivs. were synthesized by conjugation to bile acids, sterols, and alkanolic acids. The hydrophobicity of the heparin derivs. depended on the feed mole ratio of heparin to hydrophobic agent. The heparin derivs. were slightly hydrophobic and exhibited good soly. in a water-acetone solvent, as well as water. The heparin derivs. have a high anticoagulant activity. These slightly hydrophobic heparin derivs. can be absorbed in the gastric intestinal tract and can be used as oral dosage form. Also, the heparin derivs. can be used for surface modification to prevent coagulation on medical devices such as extracorporeal devices and implanted devices.

IT 24937-78-8, Ethylene-vinyl acetate copolymer
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (carrier; prepn. and anticoagulant activity of amphiphilic heparin conjugates)

RN 24937-78-8 HCAPLUS

CN Acetic acid ethenyl ester, polymer with ethene (9CI) (CA INDEX NAME)

CM 1

CRN 108-05-4

CMF C4 H6 O2

AcO-CH=CH₂

CM 2

CRN 74-85-1

CMF C2 H4

 $\text{H}_2\text{C}=\text{CH}_2$

IT 9005-49-6P, Heparin, biological studies

9041-08-1P, Heparin sodium

RL: IMF (Industrial manufacture); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(conjugate; prepn. and anticoagulant activity of amphiphilic heparin conjugates).

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 9041-08-1 HCAPLUS

CN Heparin, sodium salt (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 9 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1999:352563 HCAPLUS

DOCUMENT NUMBER: 131:134577

TITLE: Characterization of transient platelet contacts on a polyvinyl alcohol hydrogel by video microscopy

AUTHOR(S): Godo, Matthew N.; Sefton, Michael V.

CORPORATE SOURCE: Department of Chemical Engineering and Applied Chemistry and Centre for Biomaterials, University of Toronto, Toronto, ON, M5S 3E5, Can.

SOURCE: Biomaterials (1999), 20(12), 1117-1126

CODEN: BIMADU; ISSN: 0142-9612

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Acridine orange labeled, washed human platelets were counted and tracked on polyvinyl alc. (PVA), heparin-PVA and polyethylene (PE)-coated coverslips with a view to understand why transient contact on the PVA hydrogels lead to elevated platelet activation and consumption relative to polyethylene. Over the 4 min of initial contact that was studied, platelet adhesion was higher on PE than on PVA or heparin-PVA at both 40 and 200 s⁻¹, as expected, regardless of whether the surfaces were pre-treated with albumin or fibrinogen. Not all platelets appearing to make contact with the surface, actually attached. For example, less than 2% of the platelets contacting albumin pre-treated PVA (at 40 s⁻¹) remained adherent at the end of the initial 60 s observation time, while the corresponding no. for PE was greater than 9%. A greater fraction of the platelets remained adherent at the higher shear rate or with fibrinogen pre-treatment, but the difference between PVA and PE remained similar: for example, with fibrinogen pre-treatment at 200 s⁻¹, .apprx.25% of the platelet contacts resulted in adhesion on PVA while 66% did so on PE. While net platelet adhesion was less for the hydrogels, than for PE, the total no. of contacts (adherents + non-adherents) were more comparable and unexpectedly higher for albumin pre-treatment than for fibrinogen. Net platelet adhesion is but one component of the total platelet interaction with a material surface. Fluorescent video microscopy has been shown to be a useful, albeit not unequivocal, method for assessing the platelets that make contact with but do not adhere to a surface.

IT 9002-89-5, Polyvinyl alcohol

RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(characterization of transient platelet contacts on a polyvinyl alc. hydrogel by video microscopy)

RN 9002-89-5 HCAPLUS

CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5

CMF C2 H4 O

H₂C=CH-OH

IT 9005-49-6, Heparin, biological studies

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coating with poly(vinyl alc.) and; characterization of transient platelet contacts on a polyvinyl alc. hydrogel by video microscopy)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 10 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1997:150594 HCAPLUS

DOCUMENT NUMBER: 126:255386

TITLE: Development of chitosan/polyethylene vinyl acetate co-matrix: controlled release of aspirin-heparin for preventing cardiovascular thrombosis

AUTHOR(S): Vasudev, Sindhu C.; Chandy, Thomas; Sharma, Chandra P.

CORPORATE SOURCE: Div. Biosurface Technology, Sree Chitra Tirunal Inst. Med. Sci. Technology, Trivandrum, 695 012, India

SOURCE: Biomaterials (1997), 18(5), 375-381

CODEN: BIMADU; ISSN: 0142-9612

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Aspirin and heparin were embedded in chitosan/polyethylene vinyl acetate co-matrix to develop a prolonged release form. The in vitro release profiles of these drugs from the co-matrix system were monitored in Tris HCl buffer pH 7.4, using a UV spectrophotometer. The amt. of drug release was initially much higher, followed by a const. slow release profile for a prolonged period. The initial burst release was substantially modified with styrene-butadiene coatings. From SEM studies it appears that the drugs diffuse out slowly to the dissoln. medium through the micropores of the co-matrix. The released aspirin-heparin from the co-matrix system had shown their antiplatelet and anticoagulant functions. The results propose the possibility of delivering drug combinations, having synergistic effects for therapeutic applications.

IT 9005-49-6, Heparin, biological studies

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(chitosan/polyethylene vinyl acetate co-matrix for controlled release of aspirin-heparin for preventing cardiovascular thrombosis)

RN 9005-49-6 HCAPLUS

main mic.
R857.M3 B568

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 9012-76-4, Chitosan 24937-78-8, Ethylene-vinyl acetate copolymer

RL: PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(chitosan/polyethylene vinyl acetate co-matrix for controlled release of aspirin-heparin for preventing cardiovascular thrombosis)

RN 9012-76-4 HCAPLUS

CN Chitosan (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 24937-78-8 HCAPLUS

CN Acetic acid ethenyl ester, polymer with ethene (9CI) (CA INDEX NAME)

CM 1

CRN 108-05-4

CMF C4 H6 O2

AcO-CH=CH₂

CM 2

CRN 74-85-1

CMF C2 H4

H₂C=CH₂

L47 ANSWER 11 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1996:126741 HCAPLUS

DOCUMENT NUMBER: 124:156148

TITLE: Artificial blood vessel and process for producing it

INVENTOR(S): Matsuda, Takehisa; Nakajima, Nobuyuki; Kito, Hiroyuki

PATENT ASSIGNEE(S): Seikagaku Kogyo K. K., Japan

SOURCE: Can. Pat. Appl., 27 pp.

CODEN: CPXXEB

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CA 2132033	AA	19950916	CA 1994-2132033	19940914 <--
JP 07250887	A2	19951003	JP 1994-68927	19940315 <--
			JP 1994-68927	19940315

PRIORITY APPLN. INFO.:

AB This invention provides a more functionalized artificial blood vessel which can be organized by independently designing its inner and outer surfaces and endowing them with resp. different biocompatibilities, as well as a process for producing the same. The artificial blood vessel comprises a tubular support having a layer of photogelled cinnamic acid-bound chondroitin sulfate (C-CS) coated on the inner surface thereof and a layer of photogelled coumarin-bound gelatin (C-GT) coated on the outer surface thereof. The process for producing the above artificial blood vessel comprises coating a layer of coumarin-bound gelatin on the outer surface of a tubular support and a layer of cinnamic acid-bound chondroitin sulfate on the inner surface of the support and irradiating

each of the layers with light. An artificial blood vessel made of Dacron was used as a support, which was soaked in a C-GT aq. soln. and irradiated with UV light ($\lambda > 310$ nm). A C-CS aq. soln. was injected into the resulting support and internally irradiated with UV light ($\lambda > 270$ nm). The obtained blood vessel was transplanted in a dog and its biocompatibility was tested.

IT 9007-28-7DP, Chondroitin sulfate, reaction product with cinnamic acid chloride

RL: SPN (Synthetic preparation); TEM (Technical or engineered material use); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(manuf. of artificial blood vessel with inner coating of cinnamate-bound chondroitin sulfate and outer coating of coumarin-bound gelatins)

RN 9007-28-7 HCAPLUS

CN Chondroitin, hydrogen sulfate (9CI) (CA INDEX NAME)

CM 1

CRN 9007-27-6

CMF Unspecified

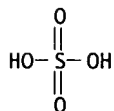
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 7664-93-9

CMF H2 O4 S



L47 ANSWER 12 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1995:307368 HCAPLUS

DOCUMENT NUMBER: 122:89343

TITLE: Study of hemodialysis materials: physicochemical and biological characterization of EVALVA, EVAPA, and heparinized EVAPA

AUTHOR(S): Barbucci, R.; Albanese, A.; Tempesti, F.; Baszkin, A.; Eloy, R.; Weill, N.; Martuscelli, E.; Cimmino, S.

CORPORATE SOURCE: CRISMA, Universita di Siena, Siena, 53100, Italy

SOURCE: Journal of Materials Science: Materials in Medicine (1994), 5(12), 844-9

CODEN: JSMMEL; ISSN: 0957-4530

PUBLISHER: Chapman & Hall

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Partially hydrolyzed ethylene/vinyl acetate copolymers were modified by the covalent binding of a heparin-complexing polymer and further heparinized in order to improve their blood compatibility. These heparinizable polymeric materials (EVAPA) were obtained by a 2-step reaction between an ethylene/vinyl alc./vinyl acetate (EVALVA) terpolymer, and the heparin complexing polymer N2LL. The physicochem. characterization of EVALVA, EVAPA and heparinized-EVAPA was carried out through thermal anal., SEM, contact angle, potentiometric measurements, water uptake and FT-IR spectroscopic measurements. The biocompatibility of the above-mentioned samples was evaluated using in vitro methods, through the detn. of heparin release in phosphate buffer soln. and in human plasma, and with the investigation of hemostasis activation.

IT 9005-49-6D, Heparin, reaction products with polyamide-polyamines and ethylene-vinyl alc.-vinyl acetate copolymer 24937-78-8D, Ethylene-vinyl acetate copolymer, hydrolyzed, reaction products with polyamide-polyamines
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (physicochem. and biol. characterization of heparinized hemodialysis polymers)
 RN 9005-49-6 HCAPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 24937-78-8 HCAPLUS
 CN Acetic acid ethenyl ester, polymer with ethene (9CI) (CA INDEX NAME)

CM 1

CRN 108-05-4
 CMF C4 H6 O2

AcO-CH=CH₂

CM 2

CRN 74-85-1
 CMF C2 H4

H₂C=CH₂

L47 ANSWER 13 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1995:307367 HCAPLUS

DOCUMENT NUMBER: 122:89342

TITLE: In situ ATR/FTIR studies of protein adsorption on polymeric materials: effectiveness of surface heparinization

AUTHOR(S): Magnani, A.; Busi, E.; Barbucci, R.

CORPORATE SOURCE: CRISMA, Universita di Siena, Siena, 53100, Italy

SOURCE: Journal of Materials Science: Materials in Medicine (1994), 5(12), 839-43

CODEN: JSMMEL; ISSN: 0957-4530

PUBLISHER: Chapman & Hall

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The adsorption of 2 proteins from human plasma (human serum albumin and human fibrinogen onto 6 different polymeric surfaces, 2 of which are heparinized), was studied by in situ ATR/FTIR spectroscopy. The different surface characteristics are reflected by different interfacial behaviors of the 2 proteins, but while both proteins unfold upon adsorption on all the different non-heparinized materials, they maintain the native conformation once adsorbed on the heparinized surfaces. These findings emphasize the effectiveness of surface heparinization.

IT 9005-49-6D, Heparin, reaction products with polyamide-polyamines 24937-78-8D, Ethylene-vinyl acetate copolymer, hydrolyzed, reaction products with polyamide-polyamines and heparin
 RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (ATR/FTIR studies of protein adsorption on heparinized polymers)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 24937-78-8 HCAPLUS

CN Acetic acid ethenyl ester, polymer with ethene (9CI) (CA INDEX NAME)

CM 1

CRN 108-05-4

CMF C4 H6 O2

AcO-CH=CH₂

CM 2

CRN 74-85-1

CMF C2 H4

H₂C=CH₂

L47 ANSWER 14 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1994:663548 HCAPLUS

DOCUMENT NUMBER: 121:263548

TITLE: Heparin surface immobilization through hydrophilic spacers: thrombin and antithrombin III binding kinetics

AUTHOR(S): Byun, Youngro; Jacobs, Harvey A.; Kim, Sung Wan

CORPORATE SOURCE: Dep. Pharmaceutics Pharmaceutical Chemistry, Univ. Utah, Salt Lake City, UT, 84108, USA

SOURCE: Journal of Biomaterials Science, Polymer Edition (1994), 6(1), 1-13
CODEN: JBSEEA; ISSN: 0920-5063

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The immobilization of heparin onto polymer surfaces using hydrophilic spacer groups has been effective in curtailing surface induced thrombus formation. In this study, the effect of hydrophilic spacers (PEO) on the binding kinetics of immobilized heparin with antithrombin III (ATIII) and thrombin was investigated. Monodispersed, low-mol. wt. heparin was fractionated on an ATIII affinity column to isolate high-ATIII affinity heparin. This high-ATIII affinity fraction was immobilized onto a styrene/p-aminostyrene random copolymer surface using hydrophilic polyethylene oxide (PEO) spacer groups. Styrene/p-aminostyrene random copolymer was chosen as the model surface to provide quant. and reproducible surface concns. of available amine groups, grafted PEO spacers, and immobilized heparin. The polymer substrate was coated onto glass beads, tolylene diisocyanate-modified PEO was covalently coupled to the surface, followed by heparin immobilization. The bioactivity of immobilized heparin was 16.2%, relative to free heparin, and a 1:1 binding ratio between heparin and PEO was achieved. The binding of ATIII and thrombin to control surfaces (no heparin), sol. heparin, heparin immobilized directly onto the surface, and heparin immobilized via spacer groups, were compared. Sol. heparin bound both thrombin and ATIII, while heparin immobilized directly onto the surface bound only thrombin. Spacer-immobilized heparin bound both ATIII and thrombin, although to a lesser extent than sol. heparin. Thus, the enhanced bioactivity of spacer-immobilized heparin, compared to direct-immobilization, may be attributed to the retention of ATIII binding.

IT 158747-37-6P

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(thrombin and antithrombin III binding to polymer-immobilized heparin surfaces)

RN 158747-37-6 HCAPLUS

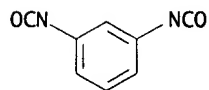
CN Heparin, polymer with 1,3-diisocyanatomethylbenzene, 4-ethenylbenzenamine, ethenylbenzene and .alpha.-hydro-.omega.-hydroxypoly(oxy-1,2-ethanediyl), graft (9CI) (CA INDEX NAME)

CM 1

CRN 26471-62-5

CMF C9 H6 N2 O2

CCI IDS



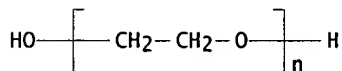
D1-Me

CM 2

CRN 25322-68-3

CMF (C2 H4 O)_n H2 O

CCI PMS



CM 3

CRN 9005-49-6

CMF Unspecified

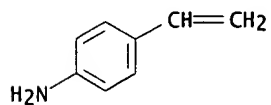
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 4

CRN 1520-21-4

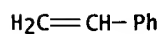
CMF C8 H9 N



CM 5

CRN 100-42-5

CMF C8 H8



L47 ANSWER 15 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1994:517492 HCAPLUS

DOCUMENT NUMBER: 121:117492

TITLE: Heparin release from polymer complex

AUTHOR(S): Kwon, Ick Chan; Bae, You Han; Kim, Sung Wan

CORPORATE SOURCE: Department of Pharmaceutics and Pharmaceutical Chemistry and Center for Controlled Chemical Delivery, University of Utah, 421 Wakaraway No. 318, Salt Lake City, UT, 84108, USA

SOURCE: Journal of Controlled Release (1994), 30(2), 155-9

CODEN: JCREEC; ISSN: 0168-3659

DOCUMENT TYPE: Journal

LANGUAGE: English

AB An electro-erodible polyelectrolyte complex was prepd. and investigated for a pulsatile drug release system. An insol. polyelectrolyte complex was formed by combining two water-sol. polymers, poly(allylamine) and heparin. Upon the application of an elec. current, a rapid structural change of the complex occurred, dissolving the polymer matrix in proportion to the intensity of an applied elec. current. The disruption of ionic bonds in the polymer matrix attached to the cathode and subsequent release of heparin was due to the locally increased pH near the cathode (resulting from hydroxyl ion prodn.). Thus, the release pattern of a model bioactive macromol., heparin, followed the applied elec. current, primarily due to surface erosion of the polymer matrix.

IT 155655-56-4

RL: BIOL (Biological study)

(heparin release from, elec. current stimulated)

RN 155655-56-4 HCAPLUS

CN Heparin, compd. with 2-propen-1-amine homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 9005-49-6

CMF Unspecified

CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 30551-89-4

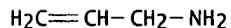
CMF (C3 H7 N)x

CCI PMS

CM 3

CRN 107-11-9

CMF C3 H7 N



L47 ANSWER 16 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1994:330933 HCAPLUS

DOCUMENT NUMBER: 120:330933

TITLE: Pulsatile drug release by electric stimulus

AUTHOR(S): Bae, You Han; Kwon, Ick Chan; Kim, Sung Wan

CORPORATE SOURCE: Cent. Controlled Chem. Delivery, Univ. Utah, Salt Lake City, UT, 84112, USA

SOURCE: ACS Symposium Series (1994), 545(Polymeric Drugs and Drug Administration), 98-110

CODEN: ACSMC8; ISSN: 0097-6156

DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Elec. currents were applied to polymeric monolithic devices to produce pulsatile drug release. The polymeric matrixes used were either elec. charged networks, or polymer-polymer complexes based on hydrogen bonding or electrostatic interactions. Pos. charged drug was released in an on-off manner from a neg. charged network. The ionically bound drug was freed from the polymer chains by ion-exchange with H⁺ ions. The polymer-polymer interactions in the formed complexes were perturbed by ionization or deionization of one part of the polymer pairs by either increasing or decreasing pH around electrodes. This resulted in polymer surface erosion and pulsatile release of the drugs entrapped in the matrixes.

IT 155655-56-4P

RL: SPN (Synthetic preparation); PREP (Preparation)
 (prepn. of, for elec. stimulus-induced drug release)

RN 155655-56-4 HCAPLUS

CN Heparin, compd. with 2-propen-1-amine homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 9005-49-6
 CMF Unspecified
 CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 30551-89-4
 CMF (C3 H7 N)x
 CCI PMS

CM 3

CRN 107-11-9
 CMF C3 H7 N

$\text{H}_2\text{C}=\text{CH}-\text{CH}_2-\text{NH}_2$

L47 ANSWER 17 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1994:307560 HCAPLUS

DOCUMENT NUMBER: 120:307560

TITLE: Medical goods coated with oligosaccharides or polysaccharides

INVENTOR(S): Uchama, Hideki; Watanabe, Junichiro

PATENT ASSIGNEE(S): Terumo Corp, Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 4 pp.

CODEN: JKXXAF

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 06086808	A2	19940329	JP 1992-238606	19920907 <--
PRIORITY APPLN. INFO.:			JP 1992-238606	19920907

AB Oligosaccharides or polysaccharides such as heparin are reduced in the presence of ammonium salts, forming amino groups at the carbohydrate terminals, and bound to functional groups of substrates via amino groups. The biol. activity of the oligosaccharides or polysaccharides are not decreased after binding to the substrates. For example, an

antithrombogenic poly(vinyl chloride) tube on which heparin had been immobilized was prepd.

IT 9005-49-6, Heparin, biological studies

RL: BIOL (Biological study)

(immobilization of, on polymer in antithrombogenic medical goods manuf.)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 9002-86-2, Poly(vinyl chloride)

RL: BIOL (Biological study)

(tubes, heparin immobilization on, in antithrombogenic medical goods manuf.)

RN 9002-86-2 HCAPLUS

CN Ethene, chloro-, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 75-01-4

CMF C2 H3 C1

H₂C=CH- C1

L47 ANSWER 18 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1994:280360 HCAPLUS

DOCUMENT NUMBER: 120:280360

TITLE: Manufacture of prosthetic materials

INVENTOR(S): Inai, Koji; Nakaji, Shuhei; Akasu, Hiroyuki

PATENT ASSIGNEE(S): Kuraray Co, Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 9 pp.

CODEN: JKXXAF

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 06063121	A2	19940308	JP 1992-224452	19920824 <--
JP 2974854	B2	19991110		

PRIORITY APPLN. INFO.: JP 1992-224452 19920824

AB An org. polymer substrate is bound to a silane crosslinking agent, a spacer, and biol. active agent, in that order to give a prosthetic material. For example, an antithrombogenic sheet was prepd. by treating a polymethylpentene sheet with 3-glycidoxypropylmethoxysilane crosslinking agent, followed by polyethyleneimine (a spacer) and aldehyde-modified heparin (an antithrombotic agent). Heparin is securely bound to the sheet for a long period while the sheet was in contact with blood plasma.

IT 9002-86-2D, Poly(vinyl chloride), reaction products with silane derivs., aldehyde-modified heparin bound, via spacer

25067-34-9D, Ethylene-vinyl alcohol copolymer, reaction products with silane derivs., heparin bound, via spacer

RL: BIOL (Biological study)

(antithrombogenic medical goods manuf. with)

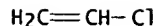
RN 9002-86-2 HCAPLUS

CN Ethene, chloro-, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 75-01-4

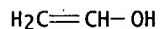
CMF C2 H3 C1



RN 25067-34-9 HCAPLUS
 CN Ethenol, polymer with ethene (9CI) (CA INDEX NAME)

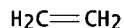
CM 1

CRN 557-75-5
 CMF C2 H4 O



CM 2

CRN 74-85-1
 CMF C2 H4



IT 9005-49-6, Heparin, uses
 RL: USES (Uses)
 (immobilization of, on crosslinked polymers, for antithrombogenic
 medical goods manuf.)

RN 9005-49-6 HCAPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 19 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1994:226845 HCAPLUS

DOCUMENT NUMBER: 120:226845

TITLE: Heparin-containing block copolymers. Part II. In vitro
 and ex vivo blood compatibility

AUTHOR(S): Vulic, I.; Okano, T.; Van Der Gaag, F. J.; Kim, S. W.;
 Feijen, J.

CORPORATE SOURCE: Dep. Chem. Technol., Univ. Twente, Enschede, 7500 AE,
 Neth.

SOURCE: Journal of Materials Science: Materials in Medicine (1993), 4(5), 448-59

CODEN: JSMMEL; ISSN: 0957-4530

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Newly synthesized heparin-contg. block copolymers, consisting of a hydrophobic block of polystyrene (PS), a hydrophilic spacer-block of poly (ethylene oxide) (PEO) and covalently bonded heparin (Hep) as bioactive block, were coated either onto glass, polydimethyl siloxane, polyurethane or PS substrates. Coated surfaces were characterized by detn. of the surface-bound heparin activity, adsorption of AT III, plasma recalcification time assays, adhesion of platelets and by an ex vivo rabbit A-A shunt model. Heparin was available at the surface of all heparin-bound surfaces to interact with AT III and thrombin and to prevent the formation of clots. The max. immobilized heparin activity was 5.5 .times. 10-3 U cm-2. Coated surfaces showed a significant prolongation of the plasma recalcification times as compared to control surfaces, due to surface-immobilized heparin. The platelet adhesion demonstrated that platelets reacted only minimally with the heparin-contg. block copolymers in the test system and that the heparin-contg. block copolymers seemed to passify the surface as compared to control surfaces. In the ex vivo A-A

shunt expts., which were carried out under low flow and low shear conditions, the heparin-contg. block copolymers exhibited prolonged occlusion times, indicating the ability of the heparin-contg. block copolymers to reduce thrombus formation at the surface.

IT 114954-84-6

RL: BIOL (Biological study)

(blood compatibility and properties of substrate-coated)

RN 114954-84-6 HCAPLUS

CN Heparin, polymer with ethenylbenzene and oxirane, block (9CI) (CA INDEX NAME)

CM 1

CRN 9005-49-6

CMF Unspecified

CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 100-42-5

CMF C8 H8

$\text{H}_2\text{C}=\text{CH}-\text{Ph}$

CM 3

CRN 75-21-8

CMF C2 H4 O



L47 ANSWER 20 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1994:137558 HCAPLUS

DOCUMENT NUMBER: 120:137558

TITLE: Photocurable glycosaminoglycan derivatives, crosslinked glycosaminoglycans and method of production thereof

INVENTOR(S): Matsuda, Takehisa; Moghaddan, Minoo J.; Sakurai, Katsukiyo

PATENT ASSIGNEE(S): Seikagaku Kogyo K. K., Japan

SOURCE: Eur. Pat. Appl., 55 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 554898	A2	19930811	EP 1993-101838	19930205 <--
EP 554898	A3	19940126		
EP 554898	B1	19970507		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 06073102	A2	19940315	JP 1992-355441	19921221 <--
JP 2855307	B2	19990210		
RU 2139886	C1	19991020	RU 1993-4491	19930203 <--
CA 2088831	AA	19930806	CA 1993-2088831	19930204 <--

HU 71625	A2	19960129	HU 1993-297	19930204 <--
HU 215503	B	19990128		
AU 9332878	A1	19930812	AU 1993-32878	19930205 <--
AU 670921	B2	19960808		
CN 1075970	A	19930908	CN 1993-102682	19930205 <--
CN 1083455	B	20020424		
US 5462976	A	19951031	US 1993-13799	19930205 <--
AT 152736	E	19970515	AT 1993-101838	19930205 <--
ES 2102537	T3	19970801	ES 1993-101838	19930205 <--
US 5763504	A	19980609	US 1995-476236	19950607 <--

PRIORITY APPLN. INFO.:

JP 1992-47744	A	19920205
JP 1992-203209	A	19920708
JP 1992-355441	A	19921221
US 1993-13799	B3	19930205

AB The title biopolymers with good physiol. compatibility and biol. degradability, useful for medical (e.g., prosthetic moldings) or pharmaceutical use (e.g., for drug slow-release coating), are prepd. based on modification of functional groups of substrates via, e.g., ester and amide linkages, using photosensitive modifiers which can be cured by free-radical mechanism. Example of a title deriv. was the cinnamate ester of hyaluronic acid which was formed by using cinnamoyl chloride in esterification; and the DMF soln.-cast film of the ester could be cured by UV light.

IT 152787-17-2

RL: USES (Uses)

(photoprepn. of crosslinked biodegradable biocompatible, for medical use)

RN 152787-17-2 HCAPLUS

CN Chondroitin, hydrogen sulfate 3-phenyl-2-propenoate, homopolymer (9CI)
(CA INDEX NAME)

CM 1

CRN 152787-16-1

CMF C9 H8 O2 . x H2 O4 S . x Unspecified

CM 2

CRN 9007-27-6

CMF Unspecified

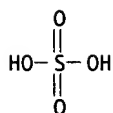
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 3

CRN 7664-93-9

CMF H2 O4 S



CM 4

CRN 621-82-9

CMF C9 H8 O2



IT 153147-07-0P

RL: PRP (Properties); PREP (Preparation)

(prepn. and properties of, photocurable, biodegradable and compatible,
for pharmaceutical and medical use)

RN 153147-07-0 HCAPLUS

CN Hyaluronic acid, 3-phenyl-2-propenoate (ester), polymer with chondroitin
hydrogen sulfate 3-phenyl-2-propenoate (9CI) (CA INDEX NAME)

CM 1

CRN 153130-78-0

CMF C9 H8 O2 . x Unspecified

CM 2

CRN 9004-61-9

CMF Unspecified

CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 3

CRN 621-82-9

CMF C9 H8 O2

Ph-CH=CH-CO₂H

CM 4

CRN 152787-16-1

CMF C9 H8 O2 . x H2 O4 S . x Unspecified

CM 5

CRN 9007-27-6

CMF Unspecified

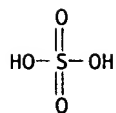
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 6

CRN 7664-93-9

CMF H2 O4 S



CM 7

CRN 621-82-9

CMF C9 H8 O2

Ph-CH=CH-CO₂H

L47 ANSWER 21 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1993:588551 HCAPLUS
 DOCUMENT NUMBER: 119:188551
 TITLE: Polyaminocations covalently immobilized on polymeric
 surfaces with polyethylene oxide spacers for
 heparin binding
 INVENTOR(S): Mohammad, Syed Fazal; Ma, Xing Hang; Kim, Sung Wan
 PATENT ASSIGNEE(S): University of Utah, USA
 SOURCE: PCT Int. Appl., 41 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9314127	A1	19930722	WO 1993-US678	19930119 <--
W: AU, BB, BG, BR, CA, DE, FI, GB, HU, JP, KP, KR, LK, MG, MN, MW, NO, PL, RO, RU, SD				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG				
AU 9335926	A1	19930803	AU 1993-35926	19930119 <--
PRIORITY APPLN. INFO.: US 1992-822715 19920121				
WO 1993-US678 19930119				
AB A compn. for removal of heparin from blood to minimize the risk of hemorrhagic complications comprises a polymeric substrate modified to contain primary amino group-contg. polycation ligands covalently bonded to the substrate through a polyethylene oxide spacer. Thus, diacid-terminated polyethylene oxide was coupled onto a cellulose acetate film and polyallylamine was reacted for immobilization. The film was placed in a heparin soln. and its heparin-binding efficacy was demonstrated.				
IT 25067-34-9D, Ethylene-vinyl alcohol copolymer, reaction products with PEO deriv. and polyaminocations 26336-38-9D, Polyvinylamine, reaction products with PEO deriv. and cellulose acetate 30551-89-4D, Polyallylamine, reaction products with PEO deriv. and cellulose acetate				
RL: BIOL (Biological study) (blood treatment with, for heparin removal)				
RN 25067-34-9 HCAPLUS				
CN Ethenol, polymer with ethene (9CI) (CA INDEX NAME)				
CM 1				
CRN 557-75-5				
CMF C2 H4 O				

H₂C=CH-OH

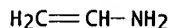
CM 2

CRN 74-85-1
 CMF C2 H4

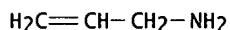
H₂C=CH₂

RN 26336-38-9 HCAPLUS
 CN Ethenamine, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 593-67-9
CMF C2 H5 NRN 30551-89-4 HCAPLUS
CN 2-Propen-1-amine, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 107-11-9
CMF C3 H7 N

IT 9005-49-6, Heparin, biological studies
 RL: REM (Removal or disposal); PROC (Process)
 (removal of, from blood, by binding with polyaminocations immobilized
 on polymeric surfaces with PEO spacers)
 RN 9005-49-6 HCAPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 22 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1993:208974 HCAPLUS
 DOCUMENT NUMBER: 118:208974
 TITLE: A method of screening for inhibitors of
 heparin-binding protein
 INVENTOR(S): Flodgaard, Hans
 PATENT ASSIGNEE(S): Novo Nordisk A/S, Den.
 SOURCE: PCT Int. Appl., 26 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9305396	A1	19930318	WO 1992-DK270	19920909 <--
W: AU, CA, CS, FI, HU, JP, PL, RU, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE				
AU 9226580	A1	19930405	AU 1992-26580	19920909 <--
EP 645016	A1	19950329	EP 1992-920351	19920909 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, SE				
JP 07504081	T2	19950511	JP 1992-504849	19920909 <--
PRIORITY APPLN. INFO.:				
			WO 1991-DK264	19910912
			WO 1992-DK270	19920909

AB Inhibitors of heparin-binding protein (HBP) are screened by incubating HBP, or a cell producing HBP, with a substance suspected of being an HBP inhibitor and with tissue, cells, or a component thereof capable of interacting with HBP, and detecting any effect of the substance on the interaction of HBP with the tissue, cells, or component thereof, decreased interaction indicating that the substance is an HBP inhibitor. Addn. of HBP to PMA-stimulated U937 cells caused a strong homotypic aggregation. Potential HBP inhibitors could be screened using the exptl. conditions described.

IT 9002-86-2, Poly(vinyl chloride) 9002-89-5,

Poly(vinyl alcohol) 9003-20-7, Poly(vinyl acetate)

RL: ANST (Analytical study)

(endothelial or smooth muscle cells or fibroblasts on solid support of, in potential heparin-binding protein inhibitor screening)

RN 9002-86-2 HCAPLUS

CN Ethene, chloro-, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 75-01-4

CMF C2 H3 C1

$\text{H}_2\text{C}=\text{CH}-\text{Cl}$

RN 9002-89-5 HCAPLUS

CN Ethene, chloro-, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5

CMF C2 H4 O

$\text{H}_2\text{C}=\text{CH}-\text{OH}$

RN 9003-20-7 HCAPLUS

CN Acetic acid ethenyl ester, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 108-05-4

CMF C4 H6 O2

$\text{AcO}-\text{CH}=\text{CH}_2$

IT 9005-49-6, Heparin, biological studies

RL: BIOL (Biological study)

(protein binding, inhibitors of, screening for, alteration of heparin-binding protein interaction with cell or tissue in)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 23 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1993:154491 HCAPLUS

DOCUMENT NUMBER: 118:154491

TITLE: Thrombin and albumin adsorption to PVA and heparin-PVA hydrogels. 2: Competition and displacement

AUTHOR(S): Smith, Barbara A. H.; Sefton, Michael V.

CORPORATE SOURCE: Dep. Chem. Eng., Univ. Toronto, Toronto, ON, M5S 1A4, Can.

SOURCE: Journal of Biomedical Materials Research (1993), 27(1), 89-95

CODEN: JBMRBG; ISSN: 0021-9304

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Thrombin adsorption to polyvinyl alc. (PVA) was different from its adsorption to polyethylene (PE), not so much in amt., but in its affinity.

Thrombin was more easily displaced from polyethylene and its adsorption was more readily prevented by prior or simultaneous exposure to albumin. From PVA (or heparin-PVA), only .apprx.30% of the adsorbed protein could be removed by a series of eluents, including even harsh ones such as 2.5M NaOH and 6M guanidine; >85% could be removed from PE. Thrombin adsorption to PVA was not affected by the presence of BSA in soln. or at the surface, but was virtually prevented on PE by preexposure to or adsorption with BSA. Heparin-PVA was not much different than PVA in most of these expts., but did exhibit a "Vroman effect". In the absence of fibrinogen or antithrombin III, there was a max. in thrombin adsorption from plasma at a plasma concn. of 1%. The behavior on this surface was dependent on both exposure time and protein concn. These studies highlight the complexity of the interaction between plasma proteins and polymer surfaces (particularly hydrogel surfaces) and the difficulty of obtaining a clear picture of what happens when a single protein interacts with a polymer in the presence of other proteins.

IT 9002-89-5, Poly(vinyl alcohol)

RL: BIOL (Biological study)

(hydrogel, albumin and thrombin adsorption to, heparinization effect on, biomaterials in relation to)

RN 9002-89-5 HCAPLUS

CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5

CMF C2 H4 O

$H_2C=CH-OH$

IT 9002-89-5D, Poly(vinyl alcohol), reaction products with heparin 9005-49-6D, Heparin, reaction products with poly(vinyl alc.)

RL: BIOL (Biological study)

(hydrogels, albumin and thrombin adsorption to, biomaterials in relation to)

RN 9002-89-5 HCAPLUS

CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5

CMF C2 H4 O

$H_2C=CH-OH$

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 24 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1993:27435 HCAPLUS

DOCUMENT NUMBER: 118:27435

TITLE: Synthesis of two novel heparinizable polymeric materials starting from an ethylene/vinyl alcohol/vinyl acetate terpolymer

AUTHOR(S): Barbucci, Rolando; Benvenuti, Manuela; Magnani, Agnese; Tempesti, Federica

CORPORATE SOURCE: Dep. Chem., Siena, 53100, Italy

SOURCE: Makromolekulare Chemie (1992), 193(12), 2979-88

DOCUMENT TYPE: CODEN: MACEAK; ISSN: 0025-116X
 Journal
 LANGUAGE: English

AB A partially hydrolyzed ethylene/vinyl acetate (EVA) copolymer was modified through the covalent binding of a heparin-complexing polymer, in order to improve its blood compatibility. Two different heparinizable polymeric materials (EVAPA I and II) were obtained by a two-step reaction between an ethylene/vinyl alc./vinyl acetate (EVALVA) terpolymer and a poly(amido-amide) (N2LL) using either hexamethylene diisocyanate (HMDI) or 1,1'-carbonyldiimidazole (CDI) as bifunctional agents, resp. EVALVA terpolymer was prepd. by a homogeneous sapon. process, and the percentage of hydrolysis was detd. by an anal. method. EVAPA I and II syntheses were followed by FT-IR/ATR (Fourier Transform IR/Attenuated Total Reflection) spectroscopy.

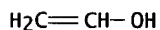
IT 25067-34-9DP, Ethylene-vinyl alcohol copolymer, sapon., reaction products with acetic anhydride and polyamidoamine
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (prepn. and heparinization of, for biomaterials)

RN 25067-34-9 HCAPLUS

CN Ethenol, polymer with ethene (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5
 CMF C2 H4 0



CM 2

CRN 74-85-1
 CMF C2 H4



IT 9005-49-6DP, Heparin, reaction products with polymer contg. sapon. ethylene-vinyl alc. copolymer and polyamidoamine

RL: SPN (Synthetic preparation); PREP (Preparation)
 (prepn. of, for biomaterials)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 9041-08-1, Heparin sodium

RL: RCT (Reactant); RACT (Reactant or reagent)
 (reaction of, with polymer contg. sapon. ethylene-vinyl alc. copolymer and polyamidosamine, for biomaterials)

RN 9041-08-1 HCAPLUS

CN Heparin, sodium salt (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 25 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1992:518449 HCAPLUS

DOCUMENT NUMBER: 117:118449

TITLE: Heparin-poly(ethylene glycol)-poly(vinyl alcohol) hydrogel: preparation and assessment of thrombogenicity

AUTHOR(S): Llanos, Gerard R.; Sefton, Michael V.

CORPORATE SOURCE: Dep. Chem. Eng. Appl. Chem., Univ. Toronto, Toronto,

SOURCE: ON, M5S 1A4, Can.
Biomaterials (1992), 13(7), 421-4 ←
CODEN: BIMADU; ISSN: 0142-9612

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Heparin was immobilized on to poly(vinyl alc.) (PVA) hydrogel through the free isocyanate end-group on a polyethylene glycol (PEG2000) which had been previously covalently linked to the hydrogel via a urethane moiety. The intention was to reduce the platelet reactivity of the PVA while also suppressing fibrin formation. Elemental nitrogen anal. revealed that the total amt. of bound heparin was 19 .mu.mol/g of dried gel. An increase in the in vitro whole blood clotting time of PVA was obsd. This was attributed to bound heparin, as the elution rate of heparin from the gel (23 pmol/m² min) was too low to produce a significant bulk concn. to interfere with fibrin formation. Ex vivo assessment using a chronic canine A-V shunt showed that the bound heparin hydrogel had no effect on the drop in the no. of platelets induced by PVA hydrogel, but increased the fractional rate of platelet destruction from approx. 0.35/day to an av. value of 0.42/day.

IT 9002-89-5DP, Polyvinyl alcohol, reaction products with polyethylene glycol and heparin 9005-49-6DP, Heparin, reaction products with polyethylene glycol and poly(vinyl alc.)

RL: SPN (Synthetic preparation); PREP (Preparation)
(hydrogels, prepn. and antithrombogenicity of, for biomaterials)

RN 9002-89-5 HCAPLUS

CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5

CMF C2 H4 O

H₂C=CH-OH

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 26 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1992:433735 HCAPLUS

DOCUMENT NUMBER: 117:33735

TITLE: Nonthrombogenic glycosaminoglycan copolymers for medical goods

INVENTOR(S): Mazid, M. Abdul; Unger, Frank M.

PATENT ASSIGNEE(S): Chembiomed Ltd., Can.

SOURCE: PCT Int. Appl., 60 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9115252	A1	19911017	WO 1991-CA120	19910410 <-- ←
W: AU, BB, BG, BR, CA, FI, HU, JP, KP, KR, LK, MC, MG, MW, NO, PL, RO, SD, SU, US				
RW: AT, BE, BF, BJ, CF, CG, CH, CM, DE, DK, ES, FR, GA, GB, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG				
CA 2080241	AA	19911011	CA 1991-2080241	19910410 <--
AU 9175637	A1	19911030	AU 1991-75637	19910410 <--
EP 524209	A1	19930127	EP 1991-906943	19910410 <--

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE
 JP 05507298 T2 19931021 JP 1991-506427 19910410 <--
 PRIORITY APPLN. INFO.: US 1990-507230 19900410
 WO 1991-CA120 19910410

AB Biocompatible glycosaminoglycan copolymers which are antithrombotic and antithrombogenic are provided for biomedical applications requiring long-term or permanent maintenance of anticoagulant properties. The novel copolymers of the invention are comprised of small fragments or segment of glycosaminoglycans such as heparin (I), which is produced by enzymic or chem. means, and copolymd. with synthetic monomeric components. Low mol. wt. I, obtained by deaminative cleavage with NO₂H, was copolymd. with 2-aminoethyl methacrylate and acrylamide to obtain an antithrombotic polymer. The ratio of antifactor Xa to activated partial thromboplastin time (indicating antithrombotic activity with respect to its anticoagulant activity) of the copolymer was 19.7.

IT 138781-13-2P 138781-14-3P 138781-16-5P
 138781-18-7P 138781-19-8P 138781-21-2P
 138781-22-3P

RL: PREP (Preparation)
 (prepn. of, for antithrombogenic medical goods)

RN 138781-13-2 HCAPLUS

CN Heparin, polymer with ethenylbenzene, graft (9CI) (CA INDEX NAME)

CM 1

CRN 9005-49-6
 CMF Unspecified
 CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 100-42-5
 CMF C8 H8

H₂C=CH-Ph

RN 138781-14-3 HCAPLUS

CN Heparin, polymer with 2-hydroxyethyl 2-methyl-2-propenoate and 2-propen-1-ol, graft (9CI) (CA INDEX NAME)

CM 1

CRN 9005-49-6
 CMF Unspecified
 CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

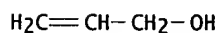
CM 2

CRN 868-77-9
 CMF C6 H10 O3

$$\begin{array}{c} \text{H}_2\text{C} \quad \text{O} \\ \parallel \quad \parallel \\ \text{Me}-\text{C}-\text{C}-\text{O}-\text{CH}_2-\text{CH}_2-\text{OH} \end{array}$$

CM 3

CRN 107-18-6
CMF C3 H6 O



RN 138781-16-5 HCAPLUS
CN Heparin, polymer with 1-ethenyl-2-pyrrolidinone and 2-propenamide, graft (9CI) (CA INDEX NAME)

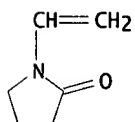
CM 1

CRN 9005-49-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

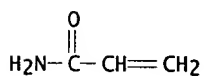
CM 2

CRN 88-12-0
CMF C6 H9 N O



CM 3

CRN 79-06-1
CMF C3 H5 N O



RN 138781-18-7 HCAPLUS
CN Heparin, polymer with N,N'-methylenebis[2-propenamide], 2-propenamide and 2-propen-1-ol, graft (9CI) (CA INDEX NAME)

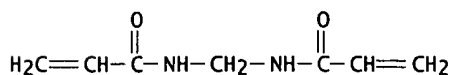
CM 1

CRN 9005-49-6
CMF Unspecified
CCI PMS, MAN

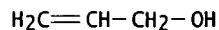
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

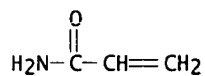
CRN 110-26-9
CMF C7 H10 N2 O2



CM 3

CRN 107-18-6
CMF C3 H6 O

CM 4

CRN 79-06-1
CMF C3 H5 N O

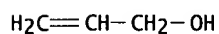
RN 138781-19-8 HCAPLUS
CN Heparin, polymer with 2-propenenitrile and 2-propen-1-ol, graft (9CI) (CA INDEX NAME)

CM 1

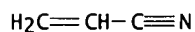
CRN 9005-49-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 107-18-6
CMF C3 H6 O

CM 3

CRN 107-13-1
CMF C3 H3 N

RN 138781-21-2 HCAPLUS
CN Heparin, polymer with 4-ethenylbenzenesulfonic acid, graft (9CI) (CA INDEX NAME)

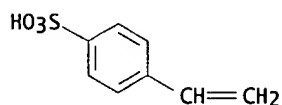
CM 1

CRN 9005-49-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 98-70-4
CMF C8 H8 O3 S



RN 138781-22-3 HCAPLUS
CN Heparin, polymer with ethenyl acetate, graft (9CI) (CA INDEX NAME)

CM 1

CRN 9005-49-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 108-05-4
CMF C4 H6 O2

AcO-CH=CH₂

L47 ANSWER 27 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1992:11171 HCAPLUS

DOCUMENT NUMBER: 116:11171

TITLE: Synthesis and nonthrombogenicity of polyetherurethaneurea film grafted with poly(sodium vinyl sulfonate)

AUTHOR(S): Ito, Yoshihiro; Iguchi, Yuichiro; Kashiwagi, Takashi; Imanishi, Yukio

CORPORATE SOURCE: Dep. Polym. Chem., Kyoto Univ., Kyoto, 606, Japan

SOURCE: Journal of Biomedical Materials Research (1991), 25(11), 1347-61

CODEN: JBMRBG; ISSN: 0021-9304

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Synthesis of nonthrombogenic materials without using biol. active substances were explored. Poly(sodium vinyl sulfonate) is a water-sol. synthetic polymer and activates antithrombin III to exert nonthrombogenicity that was dependent on the mol. wt. Polyetherurethaneurea film was plasma-treated and graft-polymd. with sodium vinyl sulfonate. The graft film showed excellent in vitro and ex vivo nonthrombogenicity by suppressing in interactions with plasma proteins and platelets as well as by inactivating blood-clotting factors.

IT 9005-49-6, Heparin, biological studies

RL: BIOL (Biological study)
(-like activity, of poly(sodium vinyl sulfonate), nonthrombogenic biomaterials in relation to)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 9002-89-5, Poly(vinyl alcohol)

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(anticoagulant activity of, biomaterial coating in relation to)
 RN 9002-89-5 HCAPLUS
 CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5
 CMF C2 H4 O

$\text{H}_2\text{C}=\text{CH}-\text{OH}$

L47 ANSWER 28 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1991:663374 HCAPLUS
 DOCUMENT NUMBER: 115:263374
 TITLE: Heparin binding on poly(L-lysine)-
 immobilized surface
 AUTHOR(S): Ma, Xinghang; Mohammad, Syed Fazal; Kim, Sung Wan
 CORPORATE SOURCE: Cent. Controlled Chem. Delivery, Univ. Utah, Salt Lake
 City, UT, 84108, USA
 SOURCE: Journal of Colloid and Interface Science (1991
), 147(1), 251-61
 CODEN: JCISA5; ISSN: 0021-9797
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB A poly(ethylene-vinyl alc.) (PEVAL) copolymer surface with immobilized
 poly(L-lysine).HBr (PLL.HBr) has been used as a model surface to study the
 interaction of heparin with polycationic surfaces. The amt. of heparin
 bound from PBS was 0.52 .mu.g/cm² on a smooth PL-immobilized PEVAL surface
 and 1.69 .mu.g/cm² on a porous PLL-PEVAL surface. Heparin adsorption
 kinetic studies indicated that heparin adsorption from plasma or blood
 exhibited a "two step" profile, which may be related to the effects of
 competitive binding between heparin and proteins, membrane porosity, and
 soln. viscosity. The time needed to reach heparin binding satn. was 10
 min in BPS and 30 min in plasma or blood at flow rate of 100 mL/min.
 However, under similar exptl. conditions, heparin binding in PBS did not
 reach satn. for 2 h at flow rate of 3 mL/min. The difference in time
 required to reach satn. for two different flow rates (3 and 100 mL/min)
 was attributed to the heparin concn. gradient between bulk and surface.
 Bound heparin was eluted with a basic soln. The recovery of heparin bound
 from PBS, plasma, and blood was 85%, which implied that most of the
 heparin was tightly bound to protonated amino groups on the side chain of
 PLL. The data suggest that electrostatic interactions between heparin and
 PLL may be the driving force for heparin binding. This study offers
 information for understanding heparin binding onto polycationic surfaces,
 esp. in biol. systems.

IT 9005-49-6, Heparin, properties
 RL: PRP (Properties)
 (binding of, to polycationic surfaces, antithrombogenic biomaterials in
 relation to)

RN 9005-49-6 HCAPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

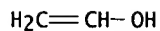
IT 25067-34-9DP, reaction product with polylysine
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (heparin binding and prepn. of, antithrombogenic biomaterials
 in relation to)

RN 25067-34-9 HCAPLUS
 CN Ethenol, polymer with ethene (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5

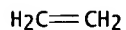
CMF C2 H4 O



CM 2

CRN 74-85-1

CMF C2 H4



IT 25067-34-9

RL: BIOL (Biological study)

(polylysine immobilization on, for heparin binding study)

RN 25067-34-9 HCAPLUS

CN Ethenol, polymer with ethene (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5

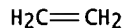
CMF C2 H4 O



CM 2

CRN 74-85-1

CMF C2 H4



IT 9002-89-5

RL: BIOL (Biological study)

(vinal fibers, ethylene-vinyl alc., polylysine
immobilization on, for heparin binding study)

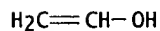
RN 9002-89-5 HCAPLUS

CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5

CMF C2 H4 O



L47 ANSWER 29 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1991:519995 HCAPLUS

DOCUMENT NUMBER: 115:119995

TITLE: Platelet consumption by polyvinyl alcohol coated
tubing in canines

AUTHOR(S): Ip, W. F.; Sefton, M. V.

CORPORATE SOURCE: Cent. Biomater., Univ. Toronto, Toronto, ON, M5S 1A4,
Can.

SOURCE: Journal of Biomedical Materials Research (1991), 25(7), 875-87
CODEN: JBMRBG; ISSN: 0021-9304

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Poly(vinyl alc.) (PVA)-coated polyethylene tubing, with or without immobilized heparin, caused severe thrombocytopenia and enhanced the prodn. of new platelets when inserted in a chronic arteriovenous shunt in canines. A similar length of uncoated polyethylene tubing neither led to thrombocytopenia nor significantly enhanced platelet regeneration, relative to the shunt only without a test section. Platelet regeneration was monitored by the malondialdehyde assay, which was assumed to make a distinction between new and old platelets. This distinction was combined with the platelet count values to enable calcn. of the cumulative consumption curve and the initial fractional consumption rate in the presence of a nonconstant platelet count. The resulting initial fractional consumption rates were: 34%/day for PVA, 20.5%/day for polyethylene, and 18%/day for the shunt only blank.

IT 9005-49-6, Heparin, biological studies
RL: BIOL (Biological study)
(blood platelet consumption by poly(vinyl alc.)-coated polyethylene tubing in relation to)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 9002-89-5, Poly(vinyl alcohol)
RL: BIOL (Biological study)
(polyethylene tubing coated with, blood platelets consumption by, heparin effect on)

RN 9002-89-5 HCAPLUS

CN Ethanol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5

CMF C2 H4 O

$$\text{H}_2\text{C}=\text{CH}-\text{OH}$$

L47 ANSWER 30 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1991:254081 HCAPLUS

DOCUMENT NUMBER: 114:254081

TITLE: Manufacture of antithrombogenic medical goods from heparin-bound poly(vinyl chloride) derivatives

INVENTOR(S): Saito, Noboru; Kashiwagi, Nobuyoshi; Sasaki, Masatomi

PATENT ASSIGNEE(S): Terumo Corp., Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 8 pp.
CODEN: JKXXAF

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 03037073	A2	19910218	JP 1989-173187	19890705 <--
PRIORITY APPLN. INFO.:			JP 1989-173187	19890705
AB Antithrombogenic medical goods are prepd. from chem. modified poly(vinyl chloride) to which heparin is bound via a coupling agent. Thus, a sheet was prepd. from NH ₂ -group-contg. poly(vinyl chloride) and treated with a soln. contg. heparin and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide-HCl				

to give an antithrombogenic sheet, which may be used in an app. for extracorporeal blood circulation and blood filtration.

IT 9005-49-6D, Heparin, poly(vinyl chloride)
deriv.-bound

RL: BIOL (Biological study)
(for antithrombogenic medical goods)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 9002-86-2D, Poly(vinyl chloride), aminated,
heparin-bound

RL: BIOL (Biological study)
(medical goods manuf. from, antithrombogenic)

RN 9002-86-2 HCAPLUS

CN Ethene, chloro-, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 75-01-4

CMF C2 H3 C1

H₂C=CH-C1

L47 ANSWER 31 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1990:618143 HCAPLUS

DOCUMENT NUMBER: 113:218143

TITLE: Inactivation of thrombin in heparin-PVA
coated tubes

AUTHOR(S): Rollason, G.; Sefton, M. V.

CORPORATE SOURCE: Cent. Biomater., Univ. Toronto, Toronto, ON, M5S 1A4,
Can.

SOURCE: Journal of Biomaterials Science, Polymer Edition (1989), 1(1), 31-41

CODEN: JBSEEA; ISSN: 0920-5063

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Heparin, immobilized on polyvinyl alc. by reaction with glutaraldehyde (heparin-PVA), retained its ability to accelerate the antithrombin III inactivation of thrombin, in a recirculating flow loop using heparin-PVA coated polyethylene tubes. The extent of inactivation, for a const. flow time, was approx. const. over ten cycles of exposure to thrombin and antithrombin III, suggesting that the immobilized heparin was reusable, as expected from the catalytic nature of non-immobilized heparin. Assessment of the chromogenic substrate activity of adsorbed thrombin and the extent of displacement were less conclusive with the implication that thrombin is adsorbed to heparin-PVA or PVA without heparin in multiple states.

IT 9002-89-5D, Poly(vinyl alcohol), reaction products with
heparin 9005-49-6D, Heparin, reaction products
with poly(vinyl alc.)

RL: BIOL (Biological study)
(polyethylene tubing coated with, inactivation of thrombin
on, biomaterials in relation to)

RN 9002-89-5 HCAPLUS

CN Ethanol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5

CMF C2 H4 O

H₂C=CH-OH

$\text{H}_2\text{C}=\text{CH}-\text{OH}$

RN 9005-49-6 HCAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 32 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1990:597870 HCAPLUS

DOCUMENT NUMBER: 113:197870

TITLE: Platelet consumption by poly(vinyl alcohol) (PVA) hydrogels and modified PVA surfaces

AUTHOR(S): Sefton, M. V.; Llanos, G.; Ip, W. F.

CORPORATE SOURCE: Dep. Chem. Eng. Appl. Chem., Univ. Toronto, Toronto, ON, M5S 1A4, Can.

SOURCE: Polymeric Materials Science and Engineering (1990), 62, 741-5

CODEN: PMSEDG; ISSN: 0743-0515

DOCUMENT TYPE: Journal

LANGUAGE: English

AB PVA hydrogels were prep'd. by covalent coupling of glutaraldehyde with PVA in the presence of MgCl_2 . Heparin was bound to these hydrogels. The interaction of heparin-PVA with blood platelets was dominated by the reactivity of the underlying substrate (PVA), the platelets appear to be consumed after transient contact with PVA (or heparin-PVA) and polyethylene oxide (PEO) was immobilized onto the PVA hydrogel by using aldehyde-terminated PEO. The PEO modification resulted in albumin adsorption and a slight redn. in consumption. Thus, PEO does not appear to be effective in reducing the platelet reactivity of PVA.

IT 9002-89-5, Poly(vinyl alcohol) 9002-89-5D, Poly(vinyl alcohol), reaction products with heparin 9005-49-6D, Heparin, reaction products with poly(vinyl alc.) hydrogels

RL: BIOL (Biological study)
(blood platelet consumption by)

RN 9002-89-5 HCAPLUS

CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5

CMF C2 H4 O

 $\text{H}_2\text{C}=\text{CH}-\text{OH}$

RN 9002-89-5 HCAPLUS

CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5

CMF C2 H4 O

 $\text{H}_2\text{C}=\text{CH}-\text{OH}$

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 33 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1990:558687 HCAPLUS
 DOCUMENT NUMBER: 113:158687
 TITLE: Controlled-release systems containing heparin
 and growth factors
 INVENTOR(S): Edelman, Elazer R.; Langer, Robert S.; Klagsburn,
 Michael; Mathiowitz, Edith
 PATENT ASSIGNEE(S): Massachusetts Institute of Technology, USA
 SOURCE: PCT Int. Appl., 24 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 8912464	A1	19891228	WO 1989-US2575	19890613 <--
W: JP				
RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
US 5100668	A	19920331	US 1988-206520	19880614 <--
PRIORITY APPLN. INFO.: US 1988-206520 19880614				
AB A system for stabilizing fibroblast-derived growth factors (FGF), maintaining their bioactivity over a prolonged period of time, and controllably releasing them for use is disclosed. The system uses growth factors bound to biocompatible substrates via heparin or heparin-derived compds. to maintain the bioactivity of the growth factors. A growth factor bound to a heparin-coated substrate can be used independently as a controlled-release device, or can be incorporated into a reservoir or matrix type controlled-release device to further enhance the controlled-release properties. FGF complexed to heparin-dextran beads and encapsulated in Na alginate capsules (allowed to harden for 5 min) was released at .apprx.1 unit/day. The released FGF retained .apprx.85% activity as detd. by a 3T3 cell synthesis assay. The release rate was .apprx.2 units/day for FGF complexed to heparin-Sepharose beads. The released FGF retained .apprx.25% activity.				
IT 9005-49-6D, Heparin, carrier conjugates, complexes with fibroblast-derived growth factor RL: BIOL (Biological study) (as controlled-release device for growth factor)				
RN 9005-49-6 HCAPLUS				
CN Heparin (8CI, 9CI) (CA INDEX NAME)				
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***				
IT 24937-78-8, Ethylene-vinyl acetate copolymer RL: BIOL (Biological study) (fibroblast-derived growth factor complex with heparin -carrier conjugate encapsulation with, for controlled release system)				
RN 24937-78-8 HCAPLUS				
CN Acetic acid ethenyl ester, polymer with ethene (9CI) (CA INDEX NAME)				

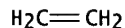
CM 1

CRN 108-05-4
 CMF C4 H6 O2

AcO-CH=CH₂

CM 2

CRN 74-85-1
 CMF C2 H4



L47 ANSWER 34 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1990:479111 HCAPLUS

DOCUMENT NUMBER: 113:79111

TITLE: Improved synthesis of polystyrene-poly(ethylene oxide)-heparin block copolymers

AUTHOR(S): Vulic, I.; Loman, A. J. B.; Feijen, J.; Okano, T.; Kim, S. W.

CORPORATE SOURCE: Dep. Chem. Technol., Univ. Twente, Enschede, Neth.

SOURCE: Journal of Polymer Science, Part A: Polymer Chemistry (1990), 28(7), 1693-720
CODEN: JPACEC; ISSN: 0887-624X

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Amino-semitelechelic polystyrene was prep'd. by anionic polymn. of styrene in cyclohexane, using sec-BuLi as initiator and N-(benzylidene)trimethylsilylamide as terminator. After purifn., polystyrene with one amino group per chain and a narrow mol. wt. distribution was obtained. The terminal amino group was used in the coupling reaction with amino-telechelic poly(ethylene oxide) using 2,4-TDI to produce amino-semitelechelic polystyrene-poly(ethylene oxide) diblock copolymer (I). Polystyrene-poly(ethylene oxide)-heparin triblock copolymer was synthesized in a DMF-H₂O (40:1) mixt. by a coupling reaction of I with HNO₂-degraded heparin at pH 7 in the presence of NaBH₃CN via reductive amination. Using this procedure, 18-32% heparin was incorporated, corresponding to .+-.1 I chain per heparin mol.

IT 114954-84-6P

RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and characterization of)

RN 114954-84-6 HCAPLUS

CN Heparin, polymer with ethenylbenzene and oxirane, block (9CI) (CA INDEX NAME)

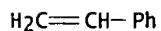
CM 1

CRN 9005-49-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 100-42-5
CMF C8 H8



CM 3

CRN 75-21-8
CMF C2 H4 O



L47 ANSWER 35 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1989:219044 HCAPLUS

DOCUMENT NUMBER: 110:219044

TITLE: In vitro platelet interactions with a heparin
-polyvinyl alcohol hydrogel

AUTHOR(S): Cholakis, Cynthia H.; Sefton, Michael V.

CORPORATE SOURCE: Dep. Chem. Eng. Appl. Chem., Univ. Toronto, Toronto,
ON, M5S 1A1, Can.SOURCE: Journal of Biomedical Materials Research (1989
) , 23(4), 399-415

CODEN: JBMRBG; ISSN: 0021-9304

DOCUMENT TYPE: Journal

LANGUAGE: English

AB No difference in in vitro platelet reactivity was found between an immobilized heparin contg. hydrogel [heparin-poly(vinyl alc.)(PVA)] and the hydrogel without heparin, in a variety of exptl. assays. There was no significant difference between the heparin-PVA- and PVA-coated polyethylene tubing in the no. of ⁵¹Cr-labeled platelets, the extent of [¹⁴C]serotonin release by the adherent platelets or in the degree of platelet count decrease after 1 h exposure to citrated canine whole blood in a Chandler loop system. Furthermore, adhesion and release values were lower than those obsd. with the uncoated polyethylene tubing (e.g., 9.3 platelets/103 .mu.g2 on PVA; 18.3 platelets/103 .mu.m2 on polyethylene). There was also no significant difference between heparin-PVA and PVA in bead column retention values with canine blood and with the previously reported washed human platelet adhesion/release values. Thus there appears to be no effect of the immobilized heparin by itself on the in vitro interactions of PVA with platelets, with the reactivity towards platelets dominated by that of the underlying substrate (i.e., PVA).

IT 9002-89-5D, Poly(vinyl alcohol), reaction products with
heparin 9005-49-6D, Heparin, reaction products
with poly(vinyl alc.)

RL: BIOL (Biological study)

(hydrogels, interaction of, with blood platelets)

RN 9002-89-5 HCAPLUS

CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5

CMF C2 H4 O

H₂C=CH-OH

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 36 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1989:199150 HCAPLUS

DOCUMENT NUMBER: 110:199150

TITLE: Effect of heparin-PVA hydrogel on platelets
in a chronic canine arterio-venous shuntAUTHOR(S): Cholakis, Cynthia H.; Zingg, Walter; Sefton, Michael
V.CORPORATE SOURCE: Dep. Chem. Eng. Appl. Chem., Univ. Toronto, Toronto,
ON, M5S 1A4, Can.SOURCE: Journal of Biomedical Materials Research (1989
) , 23(4), 417-41

CODEN: JBMRBG; ISSN: 0021-9304

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Polyvinyl alc. (PVA) hydrgel, with or without heparin, was reactive

towards canine platelets in a chronic arteriovenous shunt as demonstrated by an increase in platelet regeneration time, a systemic decrease in platelet count and transient decrease in platelet serotonin content. Immobilized heparin (heparin-PVA) had no effect whereas unmodified polyethylene was unreactive despite similar levels of platelet deposition as measured by SEM and a higher in vitro reactivity. Twenty-centimeter lengths of hydrogel coated polyethylene tubing were inserted between the arterial and venous portions of the shunt and left in place for 4-6 days, without the complicating artifacts of anticoagulation, anesthesia, or surgical intervention. Regeneration time was measured as the return to normal platelet cyclooxygenase activity after a single 240-mg dose of aspirin, with cyclooxygenase activity measured in vitro as malondialdehyde prodn. Although measuring new platelet prodn., regeneration time is an indirect measure of platelet consumption, so that the reduced regeneration time seen here was presumed to reflect enhanced material assocd. consumption and thromboembolism. Like other hydrogels, PVA does not appear to be "thromboadherent" but it does appear thrombogenic. Immobilized heparin had no addnl. effect, presumably because the platelet response was dominated by the reactivity of the underlying substrate.

IT 9002-89-5, Polyvinyl alcohol
 RL: BIOL (Biological study)
 (heparin immobilized on, hydrogels, blood platelets on
 arteriovenous shunt response to)

RN 9002-89-5 HCAPLUS

CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5

CMF C2 H4 O

H₂C=CH-OH

IT 9005-49-6, Heparin, biological studies
 RL: BIOL (Biological study)
 (immobilized on poly(vinyl alc.) hydrogels, blood platelet in
 arteriovenous shunt response to)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 37 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1989:179466 HCAPLUS

DOCUMENT NUMBER: 110:179466

TITLE: Activity toward thrombin-antithrombin of
 heparin immobilized on two hydrogels

AUTHOR(S): Tay, S. W.; Merrill, E. W.; Salzman, E. W.; Lindon, J.

CORPORATE SOURCE: Dep. Chem. Eng., MIT, Cambridge, MA, USA

SOURCE: Biomaterials (1989), 10(1), 11-15

CODEN: BIMADU; ISSN: 0142-9612

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Com. obtained (Diosynth) heparin was covalently bonded to poly(vinyl alc.) (PVA) hydrogels and to polyethylene oxide (PEO) hydrogels activated by tresyl chloride. As tresyl chloride activation of PVA increased, the specific activity of the bound heparin toward thrombin and antithrombin decreased by nearly a factor of 10 and that com. heparin bound to PEO had nearly 10-fold greater activity than when bound to PVA at comparable concns. These findings suggest that the long leash provided by PEO hydrogels may give the heparin more access to the thrombin-antithrombin pair than the tight bond to PVA, and that crowding of heparin units on a surface limits access of the thrombin-antithrombin pair.

IT 9002-89-5DP, Polyvinyl alcohol, reaction products with

heparin 9005-49-6DP, Heparin, reaction
products with polyethylene oxide or poly(vinyl alc.)
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and activity towards thrombin-antithrombin of)

RN 9002-89-5 HCAPLUS
CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5
CMF C2 H4 O

$\text{H}_2\text{C}=\text{CH}-\text{OH}$

RN 9005-49-6 HCAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 38 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1989:115443 HCAPLUS

DOCUMENT NUMBER: 110:115443

TITLE: Synthesis and characterization of polystyrene-
poly(ethylene oxide)-heparin block copolymers [Erratum
to document cited in CA109(2):7066d]

AUTHOR(S): Vulic, I.; Okano, T.; Kim, S. W.; Feijen, J.

CORPORATE SOURCE: Dep. Chem. Technol., Twente Univ. Technol., Enschede,
Neth.

SOURCE: Journal of Polymer Science, Part A: Polymer Chemistry
(1989), 27(1), 397

CODEN: JPACEC; ISSN: 0887-624X

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Errors in the addresses of the authors have been cor. The error was not
reflected in the abstr. or the index entries.

IT 114954-84-6P

RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and properties of (Erratum))

RN 114954-84-6 HCAPLUS

CN Heparin, polymer with ethenylbenzene and oxirane, block (9CI) (CA INDEX
NAME)

CM 1

CRN 9005-49-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 100-42-5
CMF C8 H8

$\text{H}_2\text{C}=\text{CH}-\text{Ph}$

CM 3

CRN 75-21-8
CMF C2 H4 O



L47 ANSWER 39 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1989:82452 HCAPLUS

DOCUMENT NUMBER: 110:82452

TITLE: Binding of heparin onto ethylene-vinyl alcohol copolymer membrane

AUTHOR(S): Shiomi, Tomoo; Satoh, Mikitoshi; Miya, Masamitsu; Imai, Kiyokazu; Akasu, Hiroyuki; Ohtake, Kazuhiko

CORPORATE SOURCE: Dep. Mater. Sci. Technol., Technol. Univ. Nagaoka, Nagaoka, 940-21, Japan

SOURCE: Journal of Biomedical Materials Research (1988), 22(A3), 269-80

CODEN: JBMRBG; ISSN: 0021-9304

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Heparin was ionically bound onto the surface of an ethylene-vinyl alc. copolymer (EVAL) membrane which was derivatized by aminoacetalization to produce cationic surface charges. The amt. of bound heparin was proportional to the ion exchange capacity of the aminoacetalized membrane and the maximal amt. obtained in this expt. was 96 U/cm² (0.59 mg/cm²). Plasma recalcification times were measured for the heparinized membrane thus obtained. Recalcification times increased proportionally with the amt. of heparin bound on the membrane, while original EVAL membranes and the non-heparinized aminoacetalized membrane did not show increases in recalcification times. This means that the heparinized EVAL membrane has a more nonthrombogenic property due to the release of heparin. The apparent amt. of heparin released from the membrane into plasma was estd. from plasma recalcification times. The release rate was 0.30-0.33 U/cm²/h (1.8 .times. 10⁻³-2.0 .times. 10⁻³ mg/cm²/h) for the membranes whose surface was considered to be satd. with heparin. The release amt. was .apprx.0.6% compared to the adsorbed heparin in the case of the 96 U/cm²-heparinized membrane incubated in plasma for 60 min.

IT 9041-08-1, Sodium heparin

RL: PROC (Process)

(binding of, to aminoacetalized ethylene-vinyl alc. copolymer membrane, thrombogenicity in relation to)

RN 9041-08-1 HCAPLUS

CN Heparin, sodium salt (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 25067-34-9D, EVAL, aminoacetalized

RL: BIOL (Biological study)

(membrane, heparin binding to, thrombogenicity in relation to)

RN 25067-34-9 HCAPLUS

CN Ethenol, polymer with ethene (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5

CMF C2 H4 O

H₂C=CH-OH

CM 2

CRN 74-85-1

BT/m1c

CMF C2 H4

 $\text{H}_2\text{C}=\text{CH}_2$

L47 ANSWER 40 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1988:498879 HCAPLUS

DOCUMENT NUMBER: 109:98879

TITLE: A method for manufacturing a hydrophilic and
heparin-containing polymer with an improved
antithrombogenic propertyINVENTOR(S): Imai, Kyokazu; Shiomi, Tomoo; Miya, Masamitsu; Akasu,
Hiroyuki; Otake, Kazuhiko

PATENT ASSIGNEE(S): Kuraray Co., Ltd., Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 7 pp.

CODEN: JKXXAF

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 62260802	A2	19871113	JP 1986-105695	19860507 <--
JP 06078382	B4	19941005		

PRIORITY APPLN. INFO.: JP 1986-105695 19860507

AB The title method involves ionically bonding heparin to an amino-group-contg. polymer prepd. by carrying out the reaction between a polymer having OH groups and RR_1NZCHO [$\text{R}, \text{R}_1 = \text{H}$ or (un)substituted C1-12 alkyl; and $\text{Z} =$ (un)substituted C4-20 alkylene or alkenyl-contg. at. group having .gtoreq.4 chain length] or its acetal compd. A fiber (15 .mu.m) 0.4 g of ethylene-vinyl alc. copolymer (sapon. degree .gtoreq.99.9%) contg. ethylene 32 mol% was dipped in an aq. soln. contg. 3-(N,N-dimethylaminopropanediamine)propionaldehyde di-Me acetal 2.5, HCl 8.0, and H_2O 73 g, subjected to a reaction at 50.degree. for 2 h, washed with a large amt. of H_2O , and dipped in an aq. soln. (55.degree.) contg. 0.1 N NaCl and heparin for 3 days to effect heparin bonding. The film showed delaying of coagulation of bovine blood serum.

IT 9005-49-6DP, Heparin, salts, reaction products of amino acetals and sapond. ethylene-vinyl acetate copolymer 24937-78-8DP, Ethylene-vinyl acetate copolymer, sapond., reaction product with amino acetals, heparinated
RL: PREP (Preparation)

(manuf. of, as prosthetic)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 24937-78-8 HCAPLUS

CN Acetic acid ethenyl ester, polymer with ethene (9CI) (CA INDEX NAME)

CM 1

CRN 108-05-4

CMF C4 H6 O2

 $\text{AcO}-\text{CH}=\text{CH}_2$

CM 2

CRN 74-85-1

CMF C2 H4

 $\text{H}_2\text{C}=\text{CH}_2$

L47 ANSWER 41 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1988:407066 HCAPLUS

DOCUMENT NUMBER: 109:7066

TITLE: Synthesis and characterization of polystyrene-poly(ethylene oxide)-heparin block copolymers

AUTHOR(S): Vulic, I.; Okano, T.; Kim, S. W.; Feijen, J.

CORPORATE SOURCE: Dep. Chem. Technol., Twente Univ. Technol., Enschede, Neth.

SOURCE: Journal of Polymer Science, Part A: Polymer Chemistry (1988), 26(2), 381-91

CODEN: JPACEC; ISSN: 0887-624X

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A procedure for the prepn. of block copolymers composed of a hydrophobic block of polystyrene, a hydrophilic spacer-block of poly(ethylene oxide) and a bioactive block of heparin was investigated. Polystyrene with one amino group per chain was synthesized by free radical oligomerization of styrene in DMF, using 2-aminoethanethiol as a chain transfer agent. This amino group was used in the coupling reaction with amino-telechelic poly(ethylene oxide) to produce an AB type diblock copolymer (I) with one amino group per polystyrene-poly(ethylene oxide) chain. The coupling of I with heparin was performed in a DMF-H₂O mixt., first by activating the heparin carboxylic groups with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide.HCl at pH 5.1-5.2 and subsequently reacting the activated carboxylic groups with the amino groups of at pH 7.5.

IT 114954-84-6P

RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation) (prepn. and properties of)

RN 114954-84-6 HCAPLUS

CN Heparin, polymer with ethenylbenzene and oxirane, block (9CI) (CA INDEX NAME)

CM 1

CRN 9005-49-6

CMF Unspecified

CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 100-42-5

CMF C8 H8

 $\text{H}_2\text{C}=\text{CH}-\text{Ph}$

CM 3

CRN 75-21-8

CMF C2 H4 O



L47 ANSWER 42 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1987:605193 HCAPLUS

DOCUMENT NUMBER: 107:205193

TITLE: Drug delivery systems based on hyaluronan, derivatives

thereof and their salts and method of producing same

INVENTOR(S): Balazs, Endre A.; Larsen, Nancy E.; Leshchiner, Adolf

PATENT ASSIGNEE(S): Biomatrix, Inc., USA

SOURCE: Eur. Pat. Appl., 30 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 224987	A2	19870610	EP 1986-306046	19860805 <--
EP 224987	A3	19871119		
EP 224987	B1	19920415		
R: BE, CH, DE, FR, GB, IT, LI, NL, SE				
AU 8660903	A1	19870604	AU 1986-60903	19860805 <--
AU 595524	B2	19900405		
CA 1340199	A1	19981215	CA 1986-516770	19860825 <--
JP 62129226	A2	19870611	JP 1986-219096	19860916 <--
JP 06092320	B4	19941116		

PRIORITY APPLN. INFO.: US 1985-804178 19851129

AB Hyaluronic acid and its derivs. are used for sustained-release of pharmaceutical substances. It may be crosslinked with divinyl sulfone, or may be a viscoelastic putty. It is useful for topical products such as eye drops. Na hyaluronate 0.58 g was swelled with water 20 mL for 20 h and treated with aq. NaOH and crosslinked with divinylsulfone. The gel was placed in an NaCl-phosphate buffer and dialyzed against 0.15 M NaCl for 5 days. The crosslinked hyaluronic acid concn. was 0.21%; this gel was mixed with mydriacyl to a concn. of 0.5%. Rabbits treated with this mydriacyl-hyaluronic acid compn. maintained a >50% pupil size increase for .apprx.340 min., compared to 240 min. for controls treated with mydriacyl in salts soln. The role of pupil size decrease was also slower in test rabbits, indicating the combination of a drug with hyaluronic acid gel significantly prolonged the period of effectiveness of the drug.

IT 111307-33-6P

RL: PREP (Preparation)

(prepn. of, for sustained drug release system)

RN 111307-33-6 HCAPLUS

CN Hyaluronic acid, sodium salt, polymer with chondroitin hydrogen sulfate and 1,1'-sulfonylbis[ethene] (9CI) (CA INDEX NAME)

CM 1

CRN 9067-32-7

CMF Unspecified

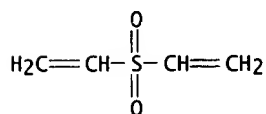
CCI PMS, MAN

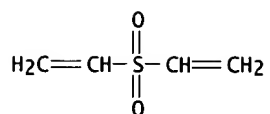
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 77-77-0

CMF C4 H6 O2 S





CM 3

CRN 9007-28-7

CMF H2 O4 S . x Unspecified

CM 4

CRN 9007-27-6

CMF Unspecified

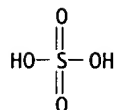
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 5

CRN 7664-93-9

CMF H2 O4 S



L47 ANSWER 43 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1986:632207 HCAPLUS

DOCUMENT NUMBER: 105:232207

TITLE: Crosslinked gels of hyaluronic acid and products containing these gels for cosmetics and pharmaceuticals

INVENTOR(S): Balazs, Endre A.; Leshchiner, Adolf

PATENT ASSIGNEE(S): Biomatrix, Inc., USA

SOURCE: U.S., 10 pp.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4582865	A	19860415	US 1984-678895	19841206 <--
US 4636524	A	19870113	US 1985-709977	19850308 <--
CA 1230186	A1	19871208	CA 1985-481055	19850508 <--
GB 2168067	A1	19860611	GB 1985-12072	19850513 <--
GB 2168067	B2	19890607		
AU 8543045	A1	19860612	AU 1985-43045	19850528 <--
AU 569157	B2	19880121		
FR 2574414	A1	19860613	FR 1985-7941	19850528 <--
FR 2574414	B1	19870703		
DE 3520008	A1	19860619	DE 1985-3520008	19850604 <--
DE 3520008	C2	19911010		
JP 61138601	A2	19860626	JP 1985-147612	19850704 <--
JP 04030961	B4	19920525		
SE 8503486	A	19860607	SE 1985-3486	19850715 <--

SE 460792	B	19891120		
SE 460792	C	19900315		
US 4605691	A	19860812	US 1985-755976	19850718 <--
GB 2181147	A1	19870415	GB 1986-18719	19860731 <--
GB 2181147	B2	19890607		
GB 2181148	A1	19870415	GB 1986-18720	19860731 <--
GB 2181148	B2	19890607		
AU 8772173	A1	19870827	AU 1987-72173	19870428 <--
AU 572419	B2	19880505		
GB 2205848	A1	19881221	GB 1988-17772	19880726 <--
GB 2205848	B2	19890524		
SE 8901672	A	19890510	SE 1989-1672	19890510 <--
SE 501828	C2	19950522		
JP 02138346	A2	19900528	JP 1989-232667	19890906 <--
JP 06037575	B4	19940518		
US 5128326	A	19920707	US 1990-559413	19900723 <--

PRIORITY APPLN. INFO.:

US 1984-678895	19841206
US 1985-709977	19850308
GB 1985-12072	19850513
US 1985-755976	19850718
US 1985-804178	19851129
US 1988-140877	19880106
US 1989-320822	19890309

AB Mixed crosslinked gels of hyaluronic acid and .gtoreq.1 other hydrophilic polymer having a functional group capable of reacting with divinyl sulfone is prepd. by subjecting a mixt. of Na hyaluronate and the other hydrophilic polymer in a dil. aq. alk. soln. at a pH .gtoreq.9 to a crosslinking reaction with divinyl sulfone at .apprx.20.degree.. The gels may contain an inert water-insol. substance, e.g., a hydrocarbon, an oil or fat, a pigment, polyethylene, or poly(tetrafluoroethylene), or covalently bonded low mol. wt. substances such as drugs, esp. carminic acid. These products are useful in cosmetic formulations and as drug delivery systems. Thus, a cosmetic formulation contained crosslinked gel 90, Hyloderm (1% soln. of Na hyaluronate) 5, and Polyox 1% soln. 5% by wt., had the appearance of a homogeneous viscous liq., and it gave a soft, silky feel when applied to the skin.

IT 105524-26-3

RL: BIOL (Biological study)

(as cosmetic and pharmaceutical gel network for water-insol. substances)

RN 105524-26-3 HCAPLUS

CN Hyaluronic acid, sodium salt, polymer with heparin and 1,1'-sulfonylbis[ethene] (9CI) (CA INDEX NAME)

CM 1

CRN 9067-32-7

CMF Unspecified

CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 9005-49-6

CMF Unspecified

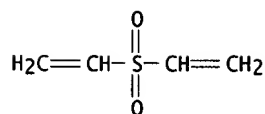
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 3

CRN 77-77-0

CMF C4 H6 O2 S



L47 ANSWER 44 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1986:485134 HCAPLUS

DOCUMENT NUMBER: 105:85134

TITLE: Coating of two polyether-polyurethanes and polyethylene with a heparin-poly(vinyl alcohol) hydrogel

AUTHOR(S): Evangelista, Ramon A.; Sefton, Michael V.

CORPORATE SOURCE: Dep. Chem. Eng. Appl. Chem., Univ. Toronto, Toronto, ON, M5S 1A4, Can.

SOURCE: Biomaterials (1986), 7(3), 206-11

CODEN: BIMADU; ISSN: 0142-9612

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Two polyether-polyurethane elastomers (Pellethane and Biomer) and polyethylene [9002-88-4] were coated with a heparin-poly(vinyl alc.) hydrogel. The requisite surface modification in prepn. for coating consisted of glow discharge cleaning and acid treatment for the polyether-polyurethanes and glow discharge cleaning and chromic acid oxidn. for polyethylene. The chem. modifications increased surface wettability. Surface anal. by attenuated total reflectance Fourier transform IR spectroscopy indicated that the acid treatment caused hydrolysis of the polyether segments of Pellethane and Biomer. Prolonged partial thromboplastin times were obsd. on the coated films. The results of Toluidine Blue assay of heparin in the soln. in which the coated films were immersed for a long time suggested that heparin was covalently bound in the coating. Such coating techniques extend the usefulness of the heparin-poly(vinyl alc.) hydrogel to a no. of medically important substrate materials.

IT 9002-89-5D, reaction products with heparin

9005-49-6D, reaction products with polyvinyl alc.

RL: BIOL (Biological study)

(coating of polyethylene and polyether-urethane rubber with, for biomaterials)

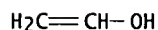
RN 9002-89-5 HCAPLUS

CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5

CMF C2 H4 O



RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 45 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1985:172602 HCAPLUS

DOCUMENT NUMBER: 102:172602

TITLE: Parallel flow arteriovenous shunt for the ex vivo evaluation of heparinized materials

AUTHOR(S): Ip, Wan Fong; Zingg, Walter; Sefton, Michael V.

CORPORATE SOURCE: Dep. Chem. Eng. Appl. Chem., Univ. Toronto, Toronto, ON, M5S 1A4, Can.

SOURCE: Journal of Biomedical Materials Research (1985
, 19(2), 161-78
CODEN: JBMRBG; ISSN: 0021-9304
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The patency of heparin-poly(vinyl alc.) (hep-PVA)-coated polyethylene tubing was longer than control tubes coated with poly(vinyl alc.) but without heparin at low flow rates in dogs using a novel parallel flow arteriovenous shunt designed to avoid surgical artifacts. A std. Silastic chronic shunt (3.18 mm internal diam., (i.d.)) was inserted between the iliac artery and vein of a dog. After a 2-wk recovery period, a small diam. coated polyethylene tube (1.14 mm i.d.) was connected in parallel with the exteriorized portion of the chronic shunt through a pair of Silastic Y-connectors, so that <3% of the shunt flow was diverted into the test tube. The chronic shunt was reused many times over a >6 mo patency period, eliminating the need for frequent surgery and reducing interanimal variability in the results. The difference in patency between heparinized and control tubes was greater at higher mainshunt flow rates indicating the presence of a significant effect of the Y-connectors on platelet adhesion or aggregation. This effect was manifested in a time-dependent redn. in circulating platelet count. SEM examn. of the midportion of the heparinized tubes after occlusion demonstrated the absence of platelet and fibrin deposits, unlike the control tubes without heparin. Although the Y-connectors played a significant role, they did not dominate the thrombotic processes occurring in this shunt and consequently the biol. effectiveness of the immobilized heparin could be demonstrated.

IT 9002-89-5

RL: BIOL (Biological study)
(heparinized polyethylene tubing coated with,
thromboresistance of, parallel flow arteriovenous shunt for evaluation
of)

RN 9002-89-5 HCAPLUS

CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5

CMF C2 H4 O

H₂C=CH-OH

IT 9005-49-6, biological studies

RL: BIOL (Biological study)
(poly(vinyl alc.)-coated polyethylene tubing contg.,
thromboresistance of, parallel flow arteriovenous shunt for evaluation
of)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 46 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1983:510715 HCAPLUS

DOCUMENT NUMBER: 99:110715

TITLE: Preparation of heparinized biomaterials

AUTHOR(S): Evangelista, Ramon; Sefton, Michael V.

CORPORATE SOURCE: Dep: Chem. Eng. Appl. Chem., Univ. Toronto, Toronto,
ON, M5S 1A4, Can.

SOURCE: Proc. IUPAC, I. U. P. A. C., Macromol. Symp., 28th (1982), 357. Int. Union Pure Appl. Chem.:
Oxford, UK.

CODEN: SODXAF

DOCUMENT TYPE: Conference

LANGUAGE: English

AB Nonthrombogenic materials were obtained by coating Pellethane, Biomer, polyethylene [9002-88-4] and Cuprophane with a heparin-poly(vinyl alc.) hydrogel. The surfaces of these polymers became more wettable after initial chem. treatment and showed good adhesion to the hydrogel. The partial thromboplastin times, measured on washed and coated polymers, confirmed that the heparinized films showed some thromboresistance. Thus, the heparinized materials are potentially useful for long-term implants.

IT 9002-89-5D, reaction products with heparin
9005-49-6D, reaction products with poly(vinyl alc.)
RL: BIOL (Biological study)
(polymers coated with, as biomaterials)

RN 9002-89-5 HCAPLUS

CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5
CMF C2 H4 O

$\text{H}_2\text{C}=\text{CH}-\text{OH}$

RN 9005-49-6 HCAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 47 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1983:132381 HCAPLUS
DOCUMENT NUMBER: 98:132381
TITLE: Production of antithrombogenic regenerated cellulose membranes
PATENT ASSIGNEE(S): Agency of Industrial Sciences and Technology, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 9 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 57162701	A2	19821006	JP 1981-46286	19810331 <--
JP 59041647	B4	19841008		

PRIORITY APPLN. INFO.: JP 1981-46286 19810331

AB Antithrombogenic membranes for hemodialysis are prepd. by treating acrylic polymer-grafted cellulose membranes with heparin, since the grafted celluloses adsorbed more heparin than celluloses themselves. Thus, a cuprammonium cellulose film (diam. 60 mm, 15 .mu.m thick, 0.45 g) was treated with an aq. soln. contg. glycidyl methacrylate, N-vinylpyrrolidone, and cerium ammonium nitrate to obtain a polymer-grafted cellulose, which was isolated, subsequently treated with heparin, and washed with water. The antithrombogenic activity of this film was tested.

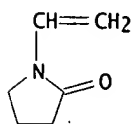
IT 9005-49-6D, reaction products with vinyl polymers and cellulose
RL: BIOL (Biological study)
(antithrombogenic dialysis membrane contg.)

RN 9005-49-6 HCAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 88-12-0D, polymers with celluloses and glycidyl methacrylate, reaction products with heparin
RL: BIOL (Biological study)
(graft, antithrombogenic dialysis membrane from)

RN 88-12-0 HCAPLUS
 CN 2-Pyrrolidinone, 1-ethenyl- (9CI) (CA INDEX NAME)



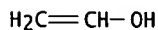
L47 ANSWER 48 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1982:461069 HCAPLUS
 DOCUMENT NUMBER: 97:61069
 TITLE: Nonthrombogenic polymers for artificial organs
 PATENT ASSIGNEE(S): Nitto Electric Industrial Co., Ltd., Japan
 SOURCE: Jpn. Kokai Tokkyo Koho, 5 pp.
 CODEN: JKXXAF
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 57075655	A2	19820512	JP 1980-153628	19801030 <--
JP 61006662	B4	19860228		

PRIORITY APPLN. INFO.: JP 1980-153628 19801030
 AB Immobilization of heparin, antithrombin III, and fibrinolysis-activating enzymes on the surface of ethylene-vinyl alc. copolymer gives nonthrombogenic materials that can be used for the prepn. of artificial organs and catheters. Thus, 1 g ethylene-vinyl alc. copolymer was suspended in 5 mL 0.1M NaHCO₃, and 50 mg heparin, 10 mg antithrombin III, and 10 mg urokinase [9039-53-6], dissolved in 10 mL 0.1M NaHCO₃, were added at 4.degree.. The copolymer immobilized 50 .mu.g heparin, 130 .mu.g antithrombin, and 100 .mu.g urokinase.
 IT 25067-34-9DP, reaction products with antithrombin III and heparin and urokinase
 RL: PREP (Preparation)
 (prepn. of, for nonthrombogenic material)
 RN 25067-34-9 HCAPLUS
 CN Ethenol, polymer with ethene (9CI) (CA INDEX NAME)

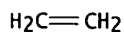
CM 1

CRN 557-75-5
 CMF C2 H4 0



CM 2

CRN 74-85-1
 CMF C2 H4



IT 9005-49-GDP; reaction products with ethylene-vinyl alc. copolymer
 RL: PREP (Preparation)

(prepn. of, for nonthromobogenic material)
 RN 9005-49-6 HCAPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 49 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1982:187142 HCAPLUS

DOCUMENT NUMBER: 96:187142

TITLE: The esterification reaction of heparin with succinic anhydride and styrene-maleic anhydride copolymer
 AUTHOR(S): Ishikawa, Yoichiro; Yamamura, Seijiro; Yoshida, Matayasu

CORPORATE SOURCE: Osaka Ind. Res. Inst., Osaka, Japan

SOURCE: Osaka Kogyo Gijutsu Shikensho Kiho (1981), 32(4), 227-31

CODEN: OKGKAE; ISSN: 0472-142X

DOCUMENT TYPE: Journal

LANGUAGE: Japanese

AB The esterification of heparin [9005-49-6] with succinic anhydride [108-30-5] or styrene-maleic anhydride copolymer (I) [9011-13-6] was examd. for prepg. heparinized materials in which the heparin not labile. The former reaction proceeded at 45.degree. in the presence or absence of a catalyst. However, at 55-65.degree., desulfation and amide formation also occurred on the amino sulfate group in heparin. The antithrombogenic activity of heparin-succinate Na salt [81544-32-3] was slightly lower than that of original heparin. Heparinized I formed a film from a THF soln. if the heparin benzyltrimethylcetylammonium salt [81507-11-1]/I ratio was <0.15, but if the ratio >0.15, gelation occurred.

IT 81544-20-9P

RL: SPN (Synthetic preparation); PREP (Preparation)

(prepn. of, nonthrombogenic biomedical polymers in relation to)

RN 81544-20-9 HCAPLUS

CN 2,5-Furandione, polymer with ethenylbenzene, ester with heparin (9CI) (CA INDEX NAME)

CM 1

CRN 9005-49-6

CMF Unspecified

CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 9011-13-6

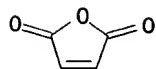
CMF (C8 H8 . C4 H2 O3)x

CCI PMS

CM 3

CRN 108-31-6

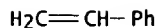
CMF C4 H2 O3



CM 4

CRN 100-42-5

CMF C8 H8



L47 ANSWER 50 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1982:40964 HCAPLUS
 DOCUMENT NUMBER: 96:40964
 TITLE: Prosthetic materials treated with anticoagulants
 PATENT ASSIGNEE(S): Nitto Electric Industrial Co., Ltd., Japan
 SOURCE: Jpn. Kokai Tokkyo Koho, 6 pp.
 CODEN: JKXXAF
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 56136564	A2	19811024	JP 1980-39927	19800327 <--
PRIORITY APPLN. INFO.:			JP 1980-39927	19800327

AB Prosthetic materials contg. heparin [9005-49-6] and antithrombin III [9000-94-6] incorporated into an ethylene-vinyl alc. copolymer [25067-34-9] prevent blood coagulation when used in artificial lungs and kidneys. For example, 1-50 .mu.g heparin and 1-50 .mu.g antithrombin/cm² were immobilized on the surface of an ethylene-vinyl alc. copolymer contg. 10-50 mol% ethylene.

IT 9005-49-6, biological studies
 RL: BIOL (Biological study)
 (ethylene-vinyl alc. copolymer contg. antithrombin III and, for artificial kidney and lung)

RN 9005-49-6 HCAPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

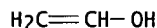
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 25067-34-9D, reaction products with antithrombin III and heparin
 RL: BIOL (Biological study)
 (for artificial kidney and lung, blood coagulation prevention in relation to)

RN 25067-34-9 HCAPLUS
 CN Ethenol, polymer with ethene (9CI) (CA INDEX NAME)

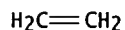
CM 1

CRN 557-75-5
 CMF C2 H4 O



CM 2

CRN 74-85-1
 CMF C2 H4



L47 ANSWER 51 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1981:575749 HCAPLUS

DOCUMENT NUMBER: 95:175749
 TITLE: Irreversible immobilization of heparin for biomaterials
 AUTHOR(S): Sefton, Michael V.; Goosen, Mattheus F. A.
 CORPORATE SOURCE: Dép. Chem. Eng. Appl. Chem., Univ. Toronto, Toronto, ON, M5S 1A4, Can.
 SOURCE: Developments in Biochemistry (1981), 12(Chem. Biol. Heparin), 463-74
 CODEN: DEBIDR; ISSN: 0165-1714
 DOCUMENT TYPE: Journal
 LANGUAGE: English.

AB The effectiveness of heparin [9005-49-6] irreversibly bound to a polymer substrate was demonstrated by both in vitro and ex vivo assays. Heparin was bound to poly(vinyl alc.) (PVA) through an acetal bridge by reaction of heparin, PVA and a mixt. of aldehydes at 70-80.degree.. The resulting gel was ground to form small beads or was applied to the hydroxylated surface of a styrene-butadiene-styrene block copolymer (SBS). The elution rate of 35S-heparin from the surface was < the detection limit (i.e., < 10⁻⁴ .mu.g/cm²min) after 60 h of washing in phosphate buffers. Nevertheless, the partial thromboplastin time of plasma incubated in tubes made from heparinized SBS was significantly greater (> 1200 s) than that with the control (120 s). Furthermore the recalcification time of plasma incubated with gels beads was prolonged in direct correlation with the amt. of gel added to the plasma. Ex vivo assays were more complex, however. At high shear rates platelet adhesion dominated with no difference being exhibited by heparinized tubing and control tubing with a PVA coating but without heparin. At very low shear rates, however, the heparinized shunt remained patent for 6 days. Exposure of a column of PVA-heparin beads to both thrombin [9002-04-4] and antithrombin [9000-94-6] III in various sequences demonstrated that thrombin binding to heparin is a primary stage in thrombin inactivation. Only when thrombin was loaded before antithrombin III was there significant inactivation of the bound thrombin. Thus it appears that despite the absence of significant heparin elution, bound heparin retains at least part of its biol. activity. Bound heparin appears to act in like manner to dissolved heparin to promote thrombin-antithrombin III complex formation.

IT 9002-89-5D, reaction products with heparin
 RL: BIOL (Biological study)
 (butadiene-styrene copolymer bound, for vascular prosthetics)

RN 9002-89-5 HCAPLUS
 CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5

CMF C2 H4 O

H₂C=CH-OH

IT 9005-49-6, properties
 RL: PRP (Properties)
 (immobilized on poly(vinyl alc.) and bound to hydroxylated butadiene-styrene copolymer surface, for vascular prosthetics)

RN 9005-49-6 HCAPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 52 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1981:521112 HCAPLUS
 DOCUMENT NUMBER: 95:121112
 TITLE: Patency of heparinized SBS shunts at high shear rates
 AUTHOR(S): Sefton, Michael V.; Zingg, Walter
 CORPORATE SOURCE: Dep. Chem. Eng. Appl. Chem., Univ. Toronto, Toronto,

SOURCE: ON, M5S 1A4, Can.
Biomaterials, Medical Devices, and Artificial Organs (1981), 9(2), 127-42
CODEN: BMDOAI; ISSN: 0090-5488

DOCUMENT TYPE: Journal
LANGUAGE: English

AB The patency of 50 cm long, 1.7 mm (internal diam.) heparin [9005-49-6]-poly(vinyl alc.) (PVA) [9002-89-5] coated Kraton rubber 1102 (SBS) arteriovenous shunts in pigs at shear rates >1000/s was not different from that of identical shunts coated with PVA but without heparin. This was attributed to the absence of any measurable effect of surface bound heparin on platelet related thrombus formation at high shear rates. On the other hand, platelet adhesion values detd. in the absence of flow by the open static method decreased with increasing heparin content in heparin-PVA films. The low overall patency (av. life of 170 min) of the PVA coated SBS shunts (with and without heparin) was related to the absence of circulating heparin during surgery and the consequent presence of tissue thromboplastin or cellular debris during the immediate postoperative period. Alternative protocols are needed to test heparinized materials at low shear rates in the absence of systemic heparin to properly assess the potential thromboresistance of such materials.

IT 9005-49-6, biological studies

RL: BIOL (Biological study)

(SBR rubber coated with poly(vinyl alc.) and, patency of, at high shear rates)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 9002-89-5

RL: BIOL (Biological study)

(SBR rubber shunts coated with heparin and, patency of, at high shear rates)

RN 9002-89-5 HCAPLUS

CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5

CMF C2 H4 O

H₂C=CH-OH

L47 ANSWER 53 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1979:409461 HCAPLUS

DOCUMENT NUMBER: 91:9461

TITLE: Heparinized styrene-butadiene-styrene elastomers

AUTHOR(S): Goosen, Mattheus F. A.; Sefton, Michael V.

CORPORATE SOURCE: Dep. Chem. Eng. Appl. Chem., Univ. Toronto, Toronto, ON, M5S 1A4, Can.

SOURCE: Journal of Biomedical Materials Research (1979), 13(3), 347-64

CODEN: JBMRBG; ISSN: 0021-9304

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A surface hydroxylated styrene-butadiene-styrene block copolymer (I) was coated with acetylated polyvinyl alc.-heparin (II) mixt. contg. glutaraldehyde and MgCl₂, and then cured at 80.degree. for 100 min to give heparinized elastomer in which polyvinyl alc. hydroxylated I, and II were covalently bound to each other by acetal bridges. II was not leached from the surface of the elastomer with 3M saline at pH 7.4. The heparinized

elastomer is potentially useful as a nonthrombogenic vascular prosthetic. Preliminary ex vivo testing, using an arteriovenous shunt, showed good thromboresistance; the shunt remained free of thrombi for >2 h, without desorption of II while the control remained patent for <15 min.

IT 9002-89-5D, reaction products with heparin and aldehydes and hydroxylated butadiene-styrene rubber 9005-49-6D, reaction products with poly(vinyl alc.) and aldehydes and hydroxylated butadiene-styrene rubber
 RL: BIOL (Biological study)
 (for nonthrombogenic vascular prosthesis)
 RN 9002-89-5 HCAPLUS
 CN Ethenol, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 557-75-5

CMF C2 H4 O

$\text{H}_2\text{C}=\text{CH}-\text{OH}$

RN 9005-49-6 HCAPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L47 ANSWER 54 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1978:547260 HCAPLUS

DOCUMENT NUMBER: 89:147260

TITLE: Heparin derivatives of high molecular weight

AUTHOR(S): Mester, L.; Amit Amaya, A.; Mester, M.

CORPORATE SOURCE: Inst. Chim. Subst. Nat., CNRS, Gif-sur-Yvette, Fr.

SOURCE: ACS Symposium Series (1978), 77(Carbohydr.

Sulfates), 113-20

CODEN: ACSMC8; ISSN: 0097-6156

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Polymn. of heparin methacrylate (I) [67712-81-6] with AIBN in dioxane gave sol. or gelatinous polymer [67770-19-8], depending on the d.p. Polymn. of I with alkyl methacrylates or vinyl compds. gave fat-sol. polymers with a higher d.p. Polymn. with crosslinking agents such as divinylbenzene or N,N'-methylenebis(acrylamide) gave polymers with completely altered mol. geometries. Structural changes in I polymer and I-Bu methacrylate copolymer [67800-50-4] were detd. by CD. The antithrombic activity of some of the high-mol. wt. polymers decreased, while the antilipemic activity increased considerably or was unchanged. The insol. polymers could be used for coating surfaces.

IT 67784-40-1P
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (prepn., properties and biol. activity of)

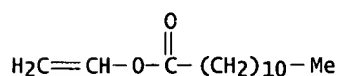
RN 67784-40-1 HCAPLUS

CN Heparin, 2-methyl-2-propenoate, polymer with ethenyl dodecanoate (9CI)
 (CA INDEX NAME)

CM 1

CRN 2146-71-6

CMF C14 H26 O2



CM 2

CRN 67712-81-6

CMF C4 H6 O2 . x Unspecified

CM 3

CRN 9005-49-6

CMF Unspecified

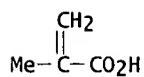
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 4

CRN 79-41-4

CMF C4 H6 O2



IT 67770-18-7

RL: USES (Uses)

(structural geometry of)

RN 67770-18-7 HCAPLUS

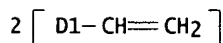
CN Heparin, 2-methyl-2-propenoate, polymer with diethenylbenzene (9CI) (CA INDEX NAME)

CM 1

CRN 1321-74-0

CMF C10 H10

CCI IDS



CM 2

CRN 67712-81-6

CMF C4 H6 O2 . x Unspecified

CM 3

CRN 9005-49-6

CMF Unspecified

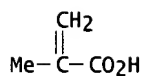
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 4

CRN 79-41-4

CMF C4 H6 O2



L47 ANSWER 55 OF 55 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1978:517856 HCAPLUS

DOCUMENT NUMBER: 89:117856

TITLE: Polymers containing amine groups and quaternary ammonium groups existing free or in salt form

INVENTOR(S): Serboli, Giancarlo; Straziota, Maurizio; La Barba, Nicolina

PATENT ASSIGNEE(S): Anic S.p.A., Italy

SOURCE: Ger. Offen., 15 pp.

CODEN: GWXXBX

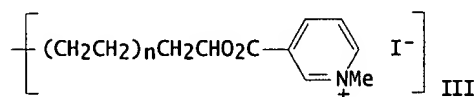
DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 2750542	A1	19780518	DE 1977-2750542	19771111 <--
CA 1092287	A1	19801223	CA 1977-289018	19771019 <--
IL 53214	A1	19820430	IL 1977-53214	19771025 <--
US 4182804	A	19800108	US 1977-847426	19771101 <--
ZA 7706556	A	19780830	ZA 1977-6556	19771103 <--
FR 2370759	A1	19780609	FR 1977-33452	19771107 <--
FR 2370759	B1	19801024		
CH 628656	A	19820315	CH 1977-13541	19771107 <--
DK 7704957	A	19780512	DK 1977-4957	19771108 <--
GB 1584078	A	19810204	GB 1977-46446	19771108 <--
SE 7712687	A	19780512	SE 1977-12687	19771109 <--
NO 7703835	A	19780512	NO 1977-3835	19771109 <--
JP 53060988	A2	19780531	JP 1977-133675	19771109 <--
BE 860735	A1	19780510	BE 1977-182557	19771110 <--
NL 7712409	A	19780516	NL 1977-12409	19771110 <--
PRIORITY APPLN. INFO.: GI			IT 1976-29235	19761111



AB The title polymers were prepd. by hydrolyzing an ethylene-vinyl acetate copolymer, contg. 26.5% vinyl acetate, to give a vinyl alc. copolymer $-(\text{CH}_2\text{CH}_2)_n(\text{CH}_2\text{CHOH})_m-$ (I), which was acylated with $\text{ClCH}_2\text{CO}_2\text{H}$ and heated with HNEt_2 to give $-(\text{CH}_2\text{CH}_2)_n(\text{CH}_2\text{CHO}_2\text{CCH}_2\text{NEt}_2)_m-$ (II). II was quaternized with undecylenic acid, and the product adsorbed on gauze for use in the treatment of mycosis. II, quaternized with sorbic acid, and used to treat the inside of fruit juice containers, improved the stability of the juices. A II film was treated with Na heparinate to give a surface heparin concn. of 0.06 mg/cm². I was also acylated with nicotinoyl chloride-HCl and quaternized with MeI to give III.

IT 24937-78-8D, hydrolyzed, esters with quaternary ammonium carboxylates

RL: BIOL (Biological study)
(as nonthrombogenic materials)

RN 24937-78-8 HCAPLUS
 CN Acetic acid ethenyl ester, polymer with ethene (9CI) (CA INDEX NAME)

CM 1

CRN 108-05-4
 CMF C4 H6 O2

AcO-CH=CH₂

CM 2

CRN 74-85-1
 CMF C2 H4

H₂C=CH₂

IT 9041-08-1
 RL: BIOL (Biological study)
 (quaternized amino ethylene-vinyl acetate copolymers
 treatment with, as nonthrombogenic materials)
 RN 9041-08-1 HCAPLUS
 CN Heparin, sodium salt (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> d cost		
COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
CONNECT CHARGES	77.33	93.27
NETWORK CHARGES	4.81	7.69
SEARCH CHARGES	0.00	109.66
DISPLAY CHARGES	247.55	259.14
	-----	-----
	329.69	469.76
CAPLUS FEE (5%)	16.24	17.13
	-----	-----
FULL ESTIMATED COST	345.93	486.89
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	-35.81	-37.11

IN FILE 'HCAPLUS' AT 16:08:57 ON 03 SEP 2003

=> log hold		
COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	345.93	486.89
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	-35.81	-37.11

SESSION WILL BE HELD FOR 60 MINUTES
 STN INTERNATIONAL SESSION SUSPENDED AT 16:09:12 ON 03 SEP 2003

Host Name:
 OK

KRISHNAN 09/937,991

Q!i5ATHZ
OK

KRISHNAN 09/937,991

=> d que

L1 8544 SEA FILE=HCAPLUS ABB=ON PLU=ON SAITO Y?/AU
 L2 2083 SEA FILE=HCAPLUS ABB=ON PLU=ON ISHIHARA M?/AU
 L3 4755 SEA FILE=HCAPLUS ABB=ON PLU=ON ONO K?/AU
 L4 4669 SEA FILE=HCAPLUS ABB=ON PLU=ON ISHIKAWA K?/AU
 L5 19976 SEA FILE=HCAPLUS ABB=ON PLU=ON (L1 OR L2 OR L3 OR L4)
 L6 32 SEA FILE=HCAPLUS ABB=ON PLU=ON L5 AND GLYCOSAMIN?
 L7 4 SEA FILE=HCAPLUS ABB=ON PLU=ON L6 AND POLYMER?
 L8 10 SEA FILE=REGISTRY ABB=ON PLU=ON (106096-93-9/BI OR 127464-60-
 2/BI OR 24967-94-0/BI OR 25322-46-7/BI OR 154531-34-7/BI OR
 83869-56-1/BI OR 9003-53-6/BI OR 9005-49-6/BI OR 9041-08-1/BI
 OR 9050-30-0/BI)
 L9 3 SEA FILE=HCAPLUS ABB=ON PLU=ON L8 AND L7

=> d ibib abs hitstr ind 1-2 (# 3 was not relevant)

L9 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2002:793739 HCAPLUS

DOCUMENT NUMBER: 137:284439

 TITLE: Glycosaminoglycan functional polymer
 and adhesion protein complexes and applications
 thereof

 INVENTOR(S): Yura, Hirofumi; Ishihara, Masayuki;
 Saito, Yoshio; Ono, Katsuaki; Sato,
 Masato

PATENT ASSIGNEE(S): Netech Inc., Japan

SOURCE: PCT Int. Appl., 34 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002081619	A1	20021017	WO 2002-JP3287	20020402
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: JP 2001-102883 A 20010402

AB It is intended to construct environment similar to an extracellular matrix
 by combining a glycosaminoglycan (GAG) functional
 polymer with a cell adhesion protein such as collagen, and the GAG
 functional polymer/protein complexes characterized in that the
 GAG functional polymer, which has a sugar chain contg. a
 structure corresponding to at least a part of the basic skeleton of GAG
 introduced into the main chain of a vinyl-type polymer, is
 carried on a cell adhesive protein; differentiation and proliferation of
 cells can be controlled in the novel material and the complexes can be
 used as cell culture materials and tissue regeneration materials.
 Heparin-carrying polystyrene (HCPS) was prepd. The HCPS efficiently bound
 to collagen-coated cell culture plate, thereby retaining the binding of
 vascular endothelial growth factor (VEGF)₁₆₅ or fibroblast growth factor
 (FGF)-2. Human umbilical vein endothelial cells showed a good adherence
 to the HCPS-bound collagen substrate.

IT 83869-56-1, GM-CSF 106096-93-9, FGF-2

127464-60-2, Vascular endothelial growth factor

154531-34-7

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(glycosaminoglycan-carrying vinyl polymers binding
with proteins and growth factor or cytokines for cell adhesion)

RN 83869-56-1 HCAPLUS

CN Colony-stimulating factor 2 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 106096-93-9 HCAPLUS

CN Fibroblast growth factor, basic (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 127464-60-2 HCAPLUS

CN Vascular endothelial growth factor (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 154531-34-7 HCAPLUS

CN Epidermal growth factor-like growth factor, heparin-binding (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 9003-53-6DP, Polystyrene, reaction products with
glycosaminoglycans 9005-49-6DP, Heparin, reaction
products with polystyrene 25322-46-7DP, Chondroitin sulfate C,
reaction products with polystyrene
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological
study); PREP (Preparation); USES (Uses)
(glycosaminoglycan-carrying vinyl polymers binding
with proteins for cell adhesion)

RN 9003-53-6 HCAPLUS

CN Benzene, ethenyl-, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 100-42-5

CMF C8 H8

H₂C=CH-Ph

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 25322-46-7 HCAPLUS

CN Chondroitin, 6-(hydrogen sulfate) (9CI) (CA INDEX NAME)

CM 1

CRN 9007-27-6

CMF Unspecified

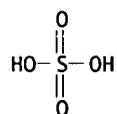
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 7664-93-9

CMF H2 O4 S



IT 9050-30-0D, Heparan sulfate, reaction products with vinyl polymers 24967-94-0D, Dermatan sulfate, reaction products with vinyl polymers
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (glycosaminoglycan-carrying vinyl polymers binding with proteins for cell adhesion)

RN 9050-30-0 HCAPLUS

CN Heparan, sulfate (9CI) (CA INDEX NAME)

CM 1

CRN 70226-44-7

CMF Unspecified

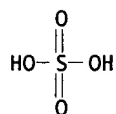
CCI MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 7664-93-9

CMF H2 O4 S



RN 24967-94-0 HCAPLUS

CN Dermatan, hydrogen sulfate (ester) (9CI) (CA INDEX NAME)

CM 1

CRN 75634-40-1

CMF Unspecified

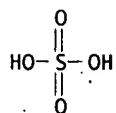
CCI MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 7664-93-9

CMF H2 O4 S



IC ICM C12M003-00

ICS C08H001-00; A61K031-726; A61K031-727; A61K038-22; A61K047-42;
 A61P043-00; A61L027-00

CC 63-7 (Pharmaceuticals)

ST glycosaminoglycan polymer protein cell adhesion

IT Cytokines

Growth factors, animal

Hepatocyte growth factor

Interleukin 3

Transforming growth factors

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(glycosaminoglycan-carrying vinyl polymers binding with proteins and growth factor or cytokines for cell adhesion)

IT Adhesion, biological
 Animal tissue culture
 Cartilage
 Human
 Regeneration, animal
 (glycosaminoglycan-carrying vinyl polymers binding
 with proteins for cell adhesion)

IT Collagens, biological studies
 Proteins
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (glycosaminoglycan-carrying vinyl polymers binding
 with proteins for cell adhesion)

IT Vinyl compounds, biological studies
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (polymers; glycosaminoglycan-carrying vinyl
 polymers binding with proteins for cell adhesion)

IT Glycosaminoglycans, biological studies
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (reaction products with vinyl polymers;
 glycosaminoglycan-carrying vinyl polymers binding
 with proteins for cell adhesion)

IT Vein
 (umbilical, endothelium; glycosaminoglycan-carrying vinyl
 polymers binding with proteins for cell adhesion)

IT 83869-56-1, GM-CSF 106096-93-9, FGF-2
 127464-60-2, Vascular endothelial growth factor
 154531-34-7
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (glycosaminoglycan-carrying vinyl polymers binding
 with proteins and growth factor or cytokines for cell adhesion)

IT 9003-53-6DP, Polystyrene, reaction products with
 glycosaminoglycans 9005-49-6DP, Heparin, reaction
 products with polystyrene 25322-46-7DP, Chondroitin sulfate C,
 reaction products with polystyrene
 RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological
 study); PREP (Preparation); USES (Uses)
 (glycosaminoglycan-carrying vinyl polymers binding
 with proteins for cell adhesion)

IT 9050-30-0D, Heparan sulfate, reaction products with vinyl
 polymers 24967-94-0D, Dermatan sulfate, reaction
 products with vinyl polymers
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (glycosaminoglycan-carrying vinyl polymers binding
 with proteins for cell adhesion)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 2000:725687 HCAPLUS
 DOCUMENT NUMBER: 133:305617
 TITLE: Functionalized glycosaminoglycan
 polymer and medical instruments and drugs by
 using the same
 INVENTOR(S): Yura, Hirofumi; Saito, Yoshio;
 Ishihara, Masayuki; Ono, Katsuaki;
 Ishikawa, Keiichi
 PATENT ASSIGNEE(S): Netech Inc., Japan
 SOURCE: PCT Int. Appl., 29 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000059967	A1	20001012	WO 2000-JP2012	20000330

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1172386 A1 20020116 EP 2000-912966 20000330

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

PRIORITY APPLN. INFO.: JP 1999-97062 A 19990402

WO 2000-JP2012 W 20000330

AB Functionalized polymers widely usable in the fields of drugs and medical instruments which are obtained by functionalizing, by org. synthesis, glycosaminoglycan controlling the adhesion, migration and proliferation of cells via binding to various cell growth factors and cytokines or direct interactions with cells. These functionalized polymers are characterized by having a sugar chain involving a structure corresponding to at least a part of the fundamental glycosaminoglycan skeleton introduced into the main chain of a vinyl polymer.

IT 106096-93-9, FGF 2 127464-60-2, Vascular endothelial growth factor

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(functionalized glycosaminoglycan polymer and medical instruments and drugs by using the same)

RN 106096-93-9 HCAPLUS

CN Fibroblast growth factor, basic (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 127464-60-2 HCAPLUS

CN Vascular endothelial growth factor (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 9041-08-1, Sodium heparin 24967-94-0, Dermatan sulfate 25322-46-7, Chondroitin sulfate c

RL: RCT (Reactant); RACT (Reactant or reagent)
(functionalized glycosaminoglycan polymer and medical instruments and drugs by using the same)

RN 9041-08-1 HCAPLUS

CN Heparin, sodium salt (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 24967-94-0 HCAPLUS

CN Dermatan, hydrogen sulfate (ester) (9CI) (CA INDEX NAME)

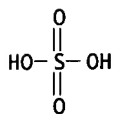
CM 1

CRN 75634-40-1
CMF Unspecified
CCI MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 7664-93-9
CMF H2 O4 S



RN 25322-46-7 HCAPLUS
 CN Chondroitin, 6-(hydrogen sulfate) (9CI) (CA INDEX NAME)

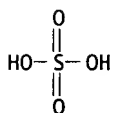
CM 1

CRN 9007-27-6
 CMF Unspecified
 CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 7664-93-9
 CMF H2 O4 S



IC ICM C08F246-00
 ICS C08F008-00; C08B037-00; A61K031-785; A61P035-00; G01N033-48;
 C12M003-00; A61L002-16
 CC 1-12 (Pharmacology)
 Section cross-reference(s): 2, 15, 63
 ST **glycosaminoglycan polymer** medical good drug
 IT Adhesion, biological
 Antitumor agents
 Medical goods
 Proliferation inhibition
 (functionalized glycosaminoglycan polymer and
 medical instruments and drugs by using the same)
 IT **Glycosaminoglycans**, biological studies
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological
 study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);
 BIOL (Biological study); PREP (Preparation); USES (Uses)
 (functionalized glycosaminoglycan polymer and
 medical instruments and drugs by using the same)
 IT **Biopolymers**
 Cytokines
 Growth factors, animal
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological
 study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
 (Uses)
 (functionalized glycosaminoglycan polymer and
 medical instruments and drugs by using the same)
 IT **Growth factors**, animal
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological
 study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
 (Uses)
 (heparin-binding; functionalized glycosaminoglycan
 polymer and medical instruments and drugs by using the same)
 IT **Mucopolysaccharides**, biological studies
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological
 study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES

(Uses)

(heparinoids; functionalized **glyc saminoglycan**
polymer and medical instruments and drugs by using the same)

IT Vinyl compounds, biological studies

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(polymers; functionalized **glycosaminoglycan**
polymer and medical instruments and drugs by using the same)

IT 106096-93-9, FGF 2 127464-60-2, Vascular endothelial growth factor

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

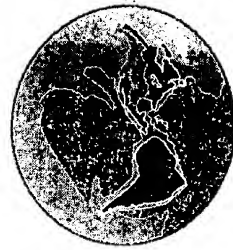
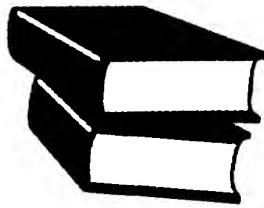
(functionalized **glycosaminoglycan polymer** and
medical instruments and drugs by using the same)

IT 9041-08-1, Sodium heparin 24967-94-0, Dermatan sulfate 25322-46-7, Chondroitin sulfate c

RL: RCT (Reactant); RACT (Reactant or reagent)

(functionalized **glycosaminoglycan polymer** and
medical instruments and drugs by using the same)

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT



Foreign Patents & Scientific Literature Branch
Examiner Document Request Form FY 2003

Last Name: KRISHNAN First Name _____

Date Assigned: 08-26-2002

TechCenter 1623 Date Completed: - -

Phone: 305-4837

Case Number: _____

Country JP Patent No. 06-510783 Pages _____ Tech Center _____

Country _____ Patent No. _____ Pages _____ Tech Center _____

Country _____ Patent No. _____ Pages _____ Tech Center _____

Country _____ Patent No. _____ Pages _____ Tech Center _____

Country _____ Patent No. _____ Pages _____ Tech Center _____

Country _____ Patent No. _____ Pages _____ Tech Center _____

Country _____ Patent No. _____ Pages _____ Tech Center _____

Country _____ Patent No. _____ Pages _____ Tech Center _____

Country _____ Patent No. _____ Pages _____ Tech Center _____

Country _____ Patent No. _____ Pages _____ Tech Center _____

Country _____ Patent No. _____ Pages _____ Tech Center _____

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(19) 日本国特許庁 (J P)

(12) 公表特許公報 (A)

(11) 特許出願公表番号

特表平6-510783

第3部門第2区分

(43) 公表日 平成6年(1994)12月1日

(51) Int. Cl. ³	識別記号	序内整理番号	F I
A 61 K 47/48	Z	7433-4C	
C 08 B 37/08	A	7433-4C	
A 61 K 31/725		9454-4C	
31/73		9454-4C	
31/785		9454-4C	

審査請求 未請求 予備審査請求 有 (全 11 頁) 最終頁に続く

(21) 出願番号	特願平5-505935	(71) 出願人	コルリーネ・システムズ・アクチエボラー グ
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(54) 【発明の名称】 新規接合体、その調製および使用ならびにその接合体を用いて調製された基体

(57) 【要約】

本発明は、多数の官能基をポリマー主鎖に沿って分布させた実質的に鎖状の有機ポリマーであって、それら官能基を介してその非活性部分中の硫酸化グリコサミノグリカン類似からの多数の分子が共有結合を通して結合されているものより成る実質的に水溶性の生化学的に活性な接合体に関する。また本発明は接合体の製造、接合体を用いた基体表面の調製、このようにして調製された基体表面および治療剤として用いるための接合体にも関する。

特表平6-510783(2)

発 明 の 説 明

1. 多数の硫酸基をポリマー主鎖に沿って分布させた實質的に線状の有機ポリマーであって、それら硫酸基を介してその非活性部分の硫酸化グリコサミノグリカン類群からの少なくとも約20分子が共有結合を通して結合されているものより成る實質的に水溶性の生物学的に活性な複合体。
2. 硫酸ポリマーが天然または合成のポリペプチド、多糖体または脂肪族ポリマーに由来する請求項1記載の複合体。
3. 硫酸ポリマーがポリリジン、ポリオルニチン、セトサン、ポリイミンまたはポリアルルアミンに由来する請求項2記載の複合体。
4. グリコサミノグリカン類が實質的に非結合を介して、好ましくは末端でポリマー主鎖に結合されている請求項1、2または3記載の複合体。
5. グリコサミノグリカン類が該グリコサミノグリカン類に結合したアミノ基を介したポリマー主鎖に結合されている請求項1〜4のいずれかに記載の複合体。
6. 複合体がそのグリコサミノグリカン類の塩に、水に溶解された場合に實質的にその全体に沿って正電荷基表面に静電的相互作用により非共价的に不可逆的に結合され得るのに十分なポリ陰イオン特性を有することを特徴とする請求項1〜5のいずれかに記載の複合体。
7. 少なくとも30グリコサミノグリカン残基を有する請求項1〜6のいずれかに記載の複合体。
8. 少なくとも100グリコサミノグリカン残基を有する請求項7記載の複合体。

に活性な複合体の調製方法。

9. 多数の硫酸基をポリマー主鎖に沿って分布させた實質的に線状の有機ポリマーであって、それら硫酸基を介して硫酸化グリコサミノグリカン類群からの多数の分子が共有結合を通して結合されているものより成る複合体を該複合体に対するソフィエーターを有する基体表面と、複合体がそこに實質的に不可逆的に結合されるように接触させることを特徴とする、硫酸化グリコサミノグリカン類による活性の調製方法。
10. 複合体がポリ陰イオン特性を有し、基体表面が陽イオン性である請求項9記載の方法。
11. 所定割合として用いるための請求項1〜12のいずれかに記載の生物学的に活性な複合体。

載の複合体。

9. 硫酸化グリコサミノグリカンがヘパリンまたはその断片または該断片である請求項1〜8のいずれかに記載の複合体。
10. グリコサミノグリカン残基が結合部位を介してポリマー主鎖に結合される請求項1〜9のいずれかに記載の複合体。
11. 硫酸化グリコサミノグリカンがヘパリンに置換結合試薬に由来する請求項10記載の複合体。
12. ポリマー主鎖がグリコサミノグリカン類のほかに少なくとも一つの付加的な生物学的に活性な物質の残基を含む請求項1〜11のいずれかに記載の複合体。
13. 複合体が多数の硫酸基をポリマー主鎖に沿って分布させた實質的に線状の有機ポリマーであって、それら硫酸基を介して硫酸化グリコサミノグリカン類群からの多数の分子が共有結合を通して結合されているものより成り、該複合体は好ましくは該複合体と基体表面との間の静電的相互作用により表面に結合されていることを特徴とする、透過ソフィエーター結合された生物学的に活性な複合体より成る調製された基体表面。
14. 生物学的に活性な複合体が請求項1〜11のいずれかに記載の複合体である請求項1記載の調製された基体表面。
15. 多数の硫酸基をポリマー主鎖に沿って分布させた實質的に線状の有機ポリマーを溶解し、そしてこれを硫酸基に、所定より結合部位を介して、その非活性部分の硫酸化グリコサミノグリカン類群からの多数の分子を共有結合的に結合させることより成ることを特徴とする、硫酸化グリコサミノグリカン類群からの多数の分子を溶解する實質的に線状の有機ポリマーより成る生物学的

明 細 書

新規複合体、その調製および使用ならびに

その複合体を用いて調製された基体

本発明は、硫酸化グリコサミノグリカンに基づく新規な生物学的に活性な複合体、その複合体の調製方法、その表面にかかる複合体を用いて調製されている基体、およびその複合体を用いた表面調製方法に関する。

硫酸化グリコサミノグリカン類は、多くの内臓硫酸化ムコ多糖類、例えばヘパリン、ヘパラン硫酸、デルマトン硫酸、コンドロイチン硫酸など多くの種々な生物学的性質を示すものの普通名である。本発明は硫酸化グリコサミノグリカン類一般に関するものであるが、以下においては、これまで医学的に最も用いられているグリコサミノグリカン、すなわちヘパリンに関する記載が大部分である。

ヘパリンは種々な哺乳動物組織、例えば肺、肝臓および脾臓の付加マトリックスで、クニパケ質に複雑に結合した形で天然に存在し、そのうち100,000までに高分子量を有しているが、市販の調製物は、硫酸および酸化方法に応じて約8,000〜20,000の範囲で変動する分子量を有している。それは交互に存在するグルクロン酸およびグルコサミン単位より成り、またその硫酸基は硫酸ロビン結合性を有する分子の特定の五糖単位に結合していることが知られている。

ヘパリンは通常ブタ膀胱膜から調製されるが、その表面調製作用の故に、血栓を溶解するための多分抗血栓作用を防止するための、剤として用いられている。前者は、とりわけ例えば血液が生計にとって異物である各異物質と接触することになる体の外の新陳代謝、い

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いわゆる体外循環（例えば人工腎臓、人工心臓装置、酸素供給器）における患者血液の処理を行うような手順、例えば腎臓透析、開心術および集中治療などにおける手順の場合に用いられる。

このような系における血液の凝固性を除く、またそれによって血餅による凝固を避けるためには高用量のヘパリンを血液に添加する必要がある。それによって凝固の危険が実質的に減り、またそれは最悪の場合には生命を脅かす状態を招きかねないことから過剰な間、そのかわりにヘパリンを表面結合することにより血液が接触する媒体によって異物である物質を固定させて両者の凝固防止作用を達成させようとする努力が払われてきている。この問題を克服した決定的契機は、ヘパリンの構造・活性相関が解明されたこと、および、ヘパリン誘導性が天然の血管壁上に後出されたことである。すなわち、この数年の間、表面結合ヘパリンを備えた系による体外循環の成功に関する報告がいくつも発表されている。

しかしながら、ヘパリンによる凝固抑制は前述の体外循環装置に用いる文脈に限定されるものではなく、血液および他の生体組織と接触する医療における様々なデバイスのバイオコンパチビリティを達成するという課題に対するより一般的の解決策として考えられるようになってきている。例えば、表面ヘパリン化は眼内レンズのバイオコンパチビリティを向上させるためにも用いられている。

ヘパリンの固定という課題に対して従来から用いられている解決策は二つの主な原理、イオン的に結合したヘパリンと共有結合的に結合したヘパリンに分けることができる。これを以下詳述する。固定化ヘパリンに基づく所望のバイオコンパチビリティを示す表面を得るにはヘパリンがその生物学的活性が保たれるように固

定されることが重要である。導入後に固定したヘパリンの生物学的活性は特定の抗トロンビン・凝血性多糖鎖にあり、血液の凝固成分との相互作用が可能となるにはその構造が表面に固定された後も完全な形で残っていなければならない。ヘパリンの固定化に関する大部分の学術論文および特許、特に1980より前に発表されたものでは、この点で満足のいくものではなく、また、その固定方法が完全なバイオコンパチブル表面を与えるかどうかの判断を可能にする標準となるとはならない。以下に、既知のヘパリン固定化方法を総述する。

I イオン的に結合したヘパリン

ヘパリンは極めて多数の負電荷基を含有しているため、ヘパリン分子は静電相互作用だけを通して陽イオン性表面に比較的強く結合することができる。適用される手段の一つは、ヘパリンをその水性溶液から陽イオン性表面処理剤で沈殿させた後、乾燥除去を有機溶媒で溶解することより成る。後者の溶媒は、高い沸点の液体（例えば dip-dry ）法に用いられる。乾燥速度を遅くするために様々な分界面活性剤が試験されている。その他の方法は第四級アンモニウム基へのヘパリンの吸着に基づいている。イオン的に結合したヘパリン表面が共通して持つ大きな短所の一つは、血液と接触しているヘパリンの溶解に関する安定性が不十分である。

B. Lora は、Bioset., Med. Dev., Int. Org., 11(1983)161-173

で特に、安定なイオン的に結合した表面の調製方法を記載している。しかしながら結合型ヘパリンはその生物学的活性を失うと報告されているが、このことは、各個ヘパリン分子があまりに強固に結合されているために抗トロンビン結合配列が血中凝固成分と相互作用し

得ないということと関係しているかもしれない。

イオン的に結合したヘパリン複合体のグルタールアルデヒドによる安定化は、例えば、310,781および45,418,485に記載されている。特許範囲にみるように、これらの調製法は完全に完全な安定な表面は得られない。従って、ヘパリンをして多分グルタールアルデヒドとの様々な反応生成物（初期の接触中に生成経路は不明）で処理する。

II. 共有結合的に結合したヘパリン

純化学的見地からは共有結合によるヘパリン固定化方法には多くの様々なものがある。しかしながら、臭化シアン、カルボジイミドおよび両者の一般的に用いられる結合試薬を用いる場合には、各ヘパリン分子が反応配列中の結合を含まないいくつかの結合により結合される。またこのためにヘパリンがその生物学的活性を失うという明らかな危険が懸念する。共有結合結合は、それに外に、常にそれは高価であり、従って最終生成物と接触させるべきでない。

しかしながら、US-4,613,665は、ヘパリンおよび他の多糖体をヘパリン分子中定置に局在する唯一の反応性アルデヒド基を介して結合する方法を記載している。この場合、ヘパリンは抗トロンビン結合配列を結合に拘束することなく共有結合的に結合させることは可能である。しかしながら、この方法では、ヘパリンを部分的に分解すること、そして微細な微粒子であるシノポリドドを最終調製工程に存在させることが必要となる。

EP-351,214は、N-脱硫酸化に付されたヘパリンの遊離アミノ基を利用することによりヘパリンを遊離アミノ基含有基表面に（例えばポリエチレンイミンまたはネトサンによる表面処理を通じて）

結合する方法を記載している。次に多官能性アルデヒド、例えばグルタールアルデヒドを用いて表面が作られる。しかしながら、グルタールアルデヒドとの反応工程は、活性配列が関与しないように確実にコントロールすることができ、また方法自体が、技術的観点からして、実用上相当価値である。

US-4,429,664は、PPGを架橋ポリマーが次いでヘパリン上の水酸基と反応するイミドイオンを含有するように反応することにより調製されたPPG-ヘパリンポリマーを記載している。この方法は、必然的にヘパリンに対し多量の非特異的結合を与え、その生物学的活性に影響を及ぼす。そのPPG-ヘパリンポリマーは純粋に重しで低い凝固活性を有しているとされている。

EP-4,284,905はヘパリンのような多糖体群をポリマーを介して結合したポリマー基体を開示している。この基体は、ポリマーポリマー表面の少数の反応性基に共有結合的に結合することによって利用可能な表面反応性基の数を増加させることにより調製される。次に反応基を具体的には限るその欠点について記したUS-4,413,665に記載の方法によって、ポリマーのカルボキシルまたはアミノ基に共有結合的に結合する。

US-4,418,490は、ヘパリンが有結合基において唯一のアセタールまたはヘミアセタール結合を通して架橋ポリマーに結合した非反応性基を含有している。一態様においては、アルデヒド基をセロースなどのポリマーに導入した後、そのアルデヒド基をヘパリン中の水酸基と反応させる。このプロセスには各ヘパリン分子の複数の水酸基が関与し、またヘパリンの生物学的に活性な配列（この配列は当該特許の出願日には実質上文献に知られた）に記載された

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りしていなかった)において水酸基が利用できることから、その遺伝配列中の水酸基も関与し、その結果最終生成物が不溶性になるという明らかな危険がある。もう一つの選択肢としての導管においては、代りにアルデヒド基を過剰な量に用いることによりヘパリンに導入する。この意味も特異性を欠き、従って結合はランダムを含むヘパリン間においてランダムに生じる。

このように、以上から明らかなように転写ヘパリン化についてこれまで知られた方法は、多かれ少かれ重大な欠点を伴っている。従って簡単に実施でき、また有害物質を含まずかつヘパリンの生体学的特性が保持された安定なヘパリン化誘導体を与える転写ヘパリン化方法が必要とされている。

ヘパリンの主要剤としての用途にもヘパリンの転写誘導体および/またはアフィニティーの故に制約がある。ヘパリンを抗凝固剤として用いる場合だけでなく、例えば血栓形成(血栓症)の発生の予防、腫瘍の増殖阻害剤として、例えば浸透性阻害剤リウマチなどのための消炎剤として、および血管形成(血管形成)調節剤としての研究された用途に用いる場合に、特にそうである。ヘパリンの種々な性質の総称は"heparin: Clinical and biological properties, Clinical applications," LaneおよびLindell編、Kendall Arnold, ロンドン、1989年にみることが出来る。従って長い半減期と増大したアフィニティーを有するヘパリン誘導体が必要とされている。

本発明によれば硫酸化グリコサミノグリカン類に基づく生物学的に両性な複合体が提供され、その複合体によって硫酸化グリコサミノグリカン類の性質を用いる物質よりもはるかに効率的に利用することができる。かかる複合体はとりわけ、複合体にアフィニティー

を有する基体表面に安定的に結合させることができ、そしてそれによって例えばヘパリンの場合には、従来の方法によるより簡単に効率的に転写ヘパリン化を行うのに用いることができる。さらに、かかる複合体は腫瘍に基づく調製物よりも長い半減期および向上したアフィニティーを有するグリコサミノグリカン誘導体を与えることができる。

ヘパリンについて記述したように、硫酸化グリコサミノグリカン類は天然にはタンパク質に結合した形で存在する。すなわち、例えばヘパリンの場合には、約15ヘパリン糖が約55アミノ酸残基のタンパク質に結合し、一方、ヘパラン硫酸を含むプロテオグリカンに配置されたヘパラン硫酸類の方はほとんどなくはるかにまばらである。実質的な複合体は結晶な形で調製することが極めて困難であり、また従来の知も限りの用途または同様の用途には適応されていない。本発明は、硫酸化グリコサミノグリカンとポリマー相対との間で半または全合成複合体を作るという発明に基づいている。この複合体は、とりわけより多くの分子の当該グリコサミノグリカンを含むことにより、個々のグリコサミノグリカン類および天然複合体よりも改善された性質を有し、またさらに相対的組成を種々な用途に適するよう調節可能に変えることができるという重要な長所を有する。

すなわち本発明は最も広い範囲において、多数の基体表面をポリマー主鎖に沿って分布させた実質的に直鎖状の有機体またはヘテロポリマーであって、それら基体表面を介してその実質的な部分の硫酸化グリコサミノグリカン類(GAG)群からの少なくとも約10分子が共有結合を通して結合されているものより成る、好ましくは、実質的に結晶な形の、少なくとも実質的に水溶性の生物学的に適合

な複合体(巨分子)を与える。

かかる複合体は既知の合成プロテオグリカンと変わることができ、その相対的組成は、調節可能に変えることができる範囲する用途に適させることができる。

本発明書における「硫酸化グリコサミノグリカン類」という用語は、その用途に通常含まれる物質、例えばヘパリン、ヘパラン硫酸、デルマタン硫酸およびコンドロイチン硫酸などのみならず、目的になった機能を果たすこれらの物質の断片および誘導体をも包含することを意味する。

グリコサミノグリカン類の阻害として機能する実質的に結晶のポリマー鎖はもろくもろくながら、自然一糖または二糖以上のグリコサミノグリカン類の結合は、少なくとも半減期の生物活性を欠くべきであるという意味において、実質的に生物学的に不溶性であるべきである。通常に溶解されるように、硫酸化グリコサミノグリカン類の結合を導致するために、そのポリマー鎖は通常に沿って分布され、そして任意に行われる実質的な結合または結合型を介してグリコサミノグリカンに結合される多くの既知の例としてアミノ、ヒドロキシまたはカルボキシル基などを有すべきである。ここで注意すべきは、当該グリコサミノグリカンがその調製方法によっては、依然として、その天然複合体タンパク質のそれに結合した未解離基を有している可能性がある、その場合結合はもろくながら有利なことからかかる基体中の例えばアミノ酸を介して行われるのである。

さらに、相対ポリマー好ましくは良好な水溶性を有すべきである。少なくともそれは、複合体について既述されたところに関

で、グリコサミノグリカン類の結合後、少なくとも実質的に水溶性であるべきである。本発明の目的に適する特定のポリマー鎖は一般に既知の基体により実質的には容易に明らかとなろう。もちろんのことながら、「実質的に結晶の」という表現の範囲内で許容されるポリマー鎖上の分枝についてもこのことはいえる。

しかしながら、好ましくは、ポリマー鎖は天然または合成のポリペプチド、多糖類または脂質性ポリマーである。発明の例としてはポリリン、ポリオルニチン、ホトリン、ポリイミンおよびポリアリンが挙げられる。

グリコサミノグリカンがポリマー鎖体に結合した後もその生物学的活性を保持することが通常望ましいという点については、各グリコサミノグリカン分子を基体で、そして単結合のみにより阻害ポリマーに結合することが望ましい。適切なには、グリコサミノグリカンはアミノ酸、好ましくはアミノ酸を介して結合されるが、グリコサミノ糖の遊離アミノ基を用いてもよい。発明は、それ自体で結晶状態で存在しているもの、あるいは既知のまたは既知のセキル化を回避させるもの。

ポリマー主鎖1個あたりのグリコサミノグリカン残基数は、前述のとおり少なくとも20であるが、好ましくはそれより多く、通常は少なくとも30である。以後に示す実施例から明らかなように、使用ポリマー主鎖によっては、ポリマー主鎖1個あたりのグリコサミノグリカン残基数は少なくとも60および100以上であってきても好ましい場合がある。上限は状況に依存し、そして、特に、選定された阻害ポリマーの溶解特性、許容される粘度の高さなどによって設定される。グリコサミノグリカン類の至適量は、特定の複合体の

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意図される用 に加え、担体ポリマーは、 にそのウイズにも修飾する。従って詳述される、接合体の基体表面への静電結合の場合には、もちろん、基体表面の電荷密度も考慮しなければならない。従って、それらグリコサミノグリカン残基は、相互に干渉しあうほどに接近した位置にあるべきではなく、さりとて、それらの間のギャップを隔すまいようにすべきである。一例として、例えば担体ポリマーとしてのポリリジンが約50,000より高い分子重を有する例が挙げられる。しかしながら、各々の特定の担体ポリマーおよび用途をそれぞれに適したグリコサミノグリカン残基は当業者により容易に決定されよう。

特にアミノ-取動性ポリマーを担体として用いる場合、場合によっては特にポリマー主鎖がグリコサミノグリカン類によってまばらにしか置換されない場合には、残った遊離アミノ基をブロックするのが好ましいことがあり、そしてこれは例えばアセチル化によって行われる。別の選択法としてのアプローチとして、所望数のアミノ基を例えばメチル基で置換してからグリコサミノグリカン類を結合させることも可能である。

既に示したとおり、本発明による新規接合体は、接合体に対する（通常はそうであるが、必ずしもグリコサミノグリカン残基に対してではない）アフィニティを有する表面に結合してよく、それによって表面に所望の生物学的特性を付与することができる。本発明の異なる観点によれば、このような調製表面は、多数の官能基をポリマー主鎖に沿って分布させた實質的に鎖状の有機ポリマーであって、それら官能基を介して置換化グリコサミノグリカン類からの多数の分子が共有結合により結合されているものより成る生物学的

に活性な接合体を適合な条件下に、接合体に対するアフィニティを有する表面と単に接触させることによって形成される。

本発明のうちの一つの観点は、多数の官能基をポリマー主鎖に沿って分布させた實質的に鎖状の有機ポリマーであって、それら官能基を介して置換化グリコサミノグリカン類からの多数の分子が共有結合により結合されているものより成る生物学的に活性な接合体を提供する。

接合体と基体表面の間の好ましい形のアフィニティは静電的性質を有するものであり、そしてより詳細にはその結合は後でより詳しく説明されるように、グリコサミノグリカン残基と基体表面の間の静電的相互作用によって生じる。

本発明による接合体のグリコサミノグリカン分子は担体ポリマーに対し大過剰なもので、この接合体は「巨大分子グリコサミノグリカン」と考えてよい。そのため、接合体1個あたりの陰イオン基数は、グリコサミノグリカン1分子あたり存在する数をはるかに上回り、その結果、接合体はそのサイズの故に、イオン性相互作用を通して陽イオン性表面に不可逆的に結合することができる。接合体を表面から遊離させるには、もちろんすべてのグリコサミノグリカン残基を同時に表面から遊離させる必要があるが、それには、「遊離」グリコサミノグリカン分子の游離に比べて相当なエネルギー供給が必要となる。

後述するある種の状態を除けば、接合体の生物学的活性はグリコサミノグリカン残基によるものと、一般的に考えられる。このような場合には、グリコサミノグリカンの数は、1個体ポリマー鎖あたりのこれらの残基の一部が同量的に陽イオン基が付与されている量

に対しては強固で不可逆的な結合を形成する一方、残りのグリコサミノグリカン類が生物学的組織、例えば血液の成分と相互作用することによりその生物学的活性を自由には調整できるようにするのに十分なるものとするべきである。

前記によるグリコサミノグリカンを付いた表面調製は、従って、共有結合とイオン性相互作用の組合せに基づくもので、このことは接合体が中間生成物として調整される（このことはすべての錯合化学操作を最終生成物とは別題に行うことができることを意味している）点で非常に有利である。更に、最終的な改修プロセスが極めて簡単となり、また調整性よく行うことができる。従って例えば本発明によるヘパリン接合体を用いた表面ヘパリン化は、前述したとおり、従来からの表面ヘパリン化方法に比べ簡単に簡略化された効率的ヘパリン化方法を提供する。以上の記載にかかわらず、もちろん、接合体を基体表面にアフィニティ阻害させた後で最終工程を所望により行ってヘパリン化表面の安定性をなお一段と向上させることもできる。

従って本発明のこの特定の観点に従って用いるための接合体は、原料の基体表面への實質的に不可逆的な結合を可能にするのに十分な静電的相互作用を有することになる。

前記に従って表面調製、例えば前記ヘパリン化すべき基体材料は、その表面が陽イオン性であるが陽イオン性にするのができる限り、基本的にバイオコンパチブル化が所望されるいずれの材料であってもよい。所望のとおり、本発明は生体にとって適合である材料、例えば各種ポリマー、金属およびセラミックスなどに適用することができる。しかしながら、本発明は生体材料、すなわち当該

グリコサミノグリカンに対するアフィニティを示す組織表面に適用することもできる。これに関連して、血液に対して最終段階の免疫反応を有する抗トロンビン結合性抗原配列を有する置換化グリコサミノグリカン類を含んでいる点に注目すると興味深い。

基体表面を陽イオン性にするための各種方法がよく知られている。後述する実施例に記すように、ポリイミンによる処理が適切な方法であることが判明しているが、他のポリアミン、例えばポリリジン、ネトサンまたはポリアルルミンなどを用いてもよい。

新規なグリコサミノグリカン接合体は、本発明の範囲内において、グリコサミノグリカン鎖のほか一またはそれ以上の他の物質、例えば別の生物学的に活性な物質の鎖を担体ポリマーに結合して含有してもよい。その場合、そのような他の生物学的に活性な物質は、グリコサミノグリカン鎖と同時あるいは別々に作用するようにしてもよい。該他の場合には、相補物質の生物学的活性だけが興味対象となり、グリコサミノグリカン類だけが基体表面に対するアフィニティ結合に利用される。従って、本発明による接合体は表面に結合させたい所望の生物学的に活性な物質のための担体としても機能し得る。グリコサミノグリカンに加えてポリマー主鎖に結合し得る物質は、成長因子、酵素、抗体、マトリックス、タンパク質、ステロイドなどである。この文脈においても、極めて特異的な免疫特性を有する接合体を、例えばグリコサミノグリカン単体に対する補体(complement)としてのモノクローナル抗体を用いて得ることができる点に注目すべきである。

所望により、かかる組合せ接合体の場合には、グリコサミノグリカンそれ自身の生物学的活性を抑制したい場合があるが、これは別

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えばヘパリンの結晶性基盤の場合には脱塩酸化により行うことができる。従って、このような場合、複合体の生物学的活性は、ポリマー主鎖に結合される相補物質の活性に完全に結合することになる。

多くの場合に、必要とはいわないまでも重要なのは複合体の表面・結合作用であるが、この作用は場合によってほとんど無害でなく、用途によってはそれを多少少なからず完全に抑制したい場合でさえあり得る。同様に、結合複合体について記載したように、特定のグリコサミノグリカン複合体の場合にもグリコサミノグリカン類の生物学的活性を除去するかまたは少なくとも低下させたい場合があり得る。場合によっては、例えばヘパリンについては、グリコサミノグリカンがいくつかの異なる生物学的作用を有することがあり、そして意図する用途に応じて一方の生物学的活性を他方を優先させるべく選択することができる。例えばヘパリンの複合は、その抗凝固作用を前述の如く脱塩酸化により阻害する一方、前述の五糖単位に結合されている他方の生物学的活性は影響されずに保たれるようにすることができる。

従って、以上より明らかなように、新規複合体の発明は、様々な用途分野に適合させるべく広い範囲にわたり変化するものである。

本発明のもう一つの観点は、多数の官能基をポリマー主鎖に付着させた実質的に線状の有機ポリマーを提供し、それら官能基に所望により結合剤によりその非選択的かつ部分的な脱塩酸化グリコサミノグリカン類からの多数の分子を非選択的に結合させることによる複合体の製造に関する。これは本発明の範囲内においていくつ

かの異なる方法によって行うことができる。

すなわち、グリコサミノグリカンは、例えば、US-4,412,565に記載の方法により調製された末端に位置するアルデヒド基を有する置換糖分解グリコサミノグリカンを以てアミノ官能性ポリマー鎖に選択結合させることができる。しかしながら、この方法は部分分解グリコサミノグリカンに限定され、また置換糖の調製の困難である。さらにまた、ポリマーがグリコサミノグリカンによって沈殿しやすいことから実際の処理も生じる。

好ましい方法によれば、代わりにグリコサミノグリカン結合剤、好ましくはヘテロ二官能性基のものによりポリマー鎖に結合する。しかしながら、例えばヒドロキシルまたはアミノ基に対する二官能性結合剤は、それぞれ分子内および分子間相互作用を強く結晶化プロパティや凝集を誘導するので、一般的に使用し難い点に注意する必要がある。

ここで、本発明による複合体をどのようにして調製できるかについての一例として、ポリリジンへのヘパリンの結合を簡単に説明する。400,000を超える分子量を有するポリリジンを選択することにより1単位分子あたり500個までのヘパリン単位を有する合成プロテオグリカンを調製することができる。この目的に適したヘテロ二官能性結合剤であるN-スクシンイミド-ε-(2-ピリジル)プロピオン酸(2BPP)をポリリジン上のアミノ基に結合し次にその2BPP-置換ポリリジンをクロマトグラフィーにより精製する。別の結合工程で2BPPは、末端アミノ酸残基中にあるいは過剰グルタミンとして存在するヘパリン上のアミノ基(後者の含量はN-脱塩酸化またはN-脱アセチル化により調製することができる)

実施例1

複合体の調製および表面・結合法学的活性試験

二つの異なるバッチのヘパリン(ヘパリン、Kab Pharmacia AB社、スウェーデン、分子量約12,000)を用いた。アミノ酸含量および遊離第一級アミノ基の相対的分布を分析し、次の結果を得た。

	アミノ酸含量 (10/40)	総遊離 (10/40)	第一級アミノ (相対的見掛け)
ヘパリンA	0.36	3.35	5,000
ヘパリンB	0.08	3.37	240

ヘパリンBの示す遊離アミノ含量が極めて低いことから、Yuko (now Glaxo), Carbohydrate Research, 46(1976)37-95に記載の方法によるN-脱塩酸化を行った。N-脱塩酸化実施後、第一級アミノ相対的見掛けで18,000という値が得られた。

ヘパリンAとヘパリンB(脱塩酸化後)をリン酸緩衝液、pH 6.5に溶解し(200mg/4ml)、それに1.5mlの2BPP(10mg/ml MeOH)を逐次添加し、そして反応を20分間進行させた。このようにして得られたSPDP-置換ヘパリンをSephadex G-25 (Pharmacia LKB Bioteknology AB社、スウェーデン)で精製した。100μlの得られた試料に500μlのジチオトレイトール(DTT, 10mg/ml)を添加し、そして得られる吸光度を230nmで分光光度法により測定した。ヘパリンAについての吸光度は0.21であり、またヘパリンB(脱塩酸化後)については0.17であった。ヘパリンに結合したSPDPはDTTを添加後クロマトグラフィーにより精製することにより58%で還元した。

450,000の分子量を有するポリリジンを水に溶解し(20mg/3ml)、そこに2mlのSPDP(10mg/ml MeOH)を添加し、そして反応を促進しながら20分間進行させた。試料はSephadex G-25 (Pharmacia LKB

にも結合される。SPDP-置換をサロチル官能基に還元後、58-置換ヘパリンをクロマトグラフィーにより精製する。ポリリジン中のSPDP基およびヘパリン中の58-基の含量はそれぞれ分光光度法により測定され、そしてヘパリンとポリリジンをSPDPおよび58に同じ等モル量を用いて混合し、ヘパリンはジスルフィド交換を介してポリリジンに共有結合的に結合されるが、その反応速度は、分光光度法により追跡することができる。驚くべきことに、ポリリジンはSPDP基が付与されている場合には、ポリリジンのアミノ基のほんの一部しか反応させていくなく、ポリリジンとヘパリンの間の沈殿反応が起らないということがわかった。にもかかわらず、実際の実験は、ジスルフィド交換が高度に選択的に行うにはM NaOH)においてのみ、より迅速でありそして従って進行することを示している。反応完了後、複合体をクロマトグラフィーにより精製して遊離ヘパリンおよび高分子還元生成物を除去する。

様々な場所でこのように調製されたヘパリン複合体の安定性に関し、驚くべきことに、ヘパリンをポリマー主鎖に結合する得られたジスルフィド橋は、グルタチオンで切断できず、低分子重量のサロチル基、例えばメルカプトニグロールなどでのみ切断し得ることがわかった。

更に、本発明によるヘパリン複合体でヘパリン化することの実際の長所は従来の方法よりも相対的に低いヘパリン原料から出発できることにある点に注目すべきである。

本発明を更に以下の実施例で説明する。

Biotechnology 48社、スウェーデン)で用剤として0.16M NaClを用いて行った。空腔(void)部分をDITで封鎖し、置換度はポリリジン1分子あたり158 SPDP基を測定された。

以上において調整されたそれぞれヘパリン-68およびポリリジン-37DPの溶液を3M NaClに調整し、そしてSPDP基に対し80%が10%過剰となるような割合で混合し、そして反応を一液進行させた。その反応混合物(ヘパリンAおよびヘパリンB(脱炭酸化合物))は完了するまで進行していたが、これはチオピリジンの遊離を242nmで分光光度法により測定された。それら混合物をSchoenclay S-500 (Pharmacia LKB Biotechnology 48社、スウェーデン)で0.5M NaClを用いて用いて精製したところ、ヘパリン-ポリリジン複合体は遊離ヘパリンに対するベースライン分離を有する鋭いピークとして現れる。ヘパリン含量はLarsson, P., et al., Biochemical J 10 (1989) 511-516に記述のオルミノールアッセイ法により測定した。

次にそれぞれのヘパリン複合体を0.5M NaClを添加したクエン酸緩衝液、pH 3.8で50mgヘパリン/μlまで希釈した。ポリエチレン(PE)チューブを次のような処理により表面-ヘパリン化した：

- 1) 過硫酸アンモニウム(1%, 60℃, 120分間)
- 2) ポリエチレンジオキサン(0.3g/μl, 室温, 15分間)
- 3) 前述の如き混合液(室温, 120分間)。

それらチューブを最後に、0.1M 過硫酸アンモニウム、pH 9で2×10分間および水で洗浄した。

表面-ヘパリン化チューブを次の方法に従ってトロンビンの吸着瓶に關して試験した。それらチューブはまずヒト血漿と共に同様に

ヘパリン-68を実施例1と同様にして調整し、そして前記において得られた高置換度のポリリジンと反応させた。反応は77%反応化まで進められ、そして、ポリリジン1個あたりのヘパリンの置換度は690:1であった。ポリエチレン(PE)のチューブを実施例1の記載と同様に調整し、試験して、次の結果が得られた。

	複合体1	複合体2
トロンビン検出 (フィブリノーゲン 除去法不使用)	0.515±0.021	0.526±0.021
トロンビン検出量 (フィブリノーゲン 除去法不使用)	0.011±0.001	0.008±0.001

これらの結果はいずれの複合体も満足できる結果を与えることを示している。

実施例3

表面-ヘパリン化体外システムの試験

次の成分で構成される体外システムを用いた：防護(ドレナージ)カテーテル(ポリ塩化ビニル(PVC))、計算カニューレ(PVC+スチール)、チュービングセット(PVC)、ポンプ駆動(エチルアルブクリレート)、加(ポリプロピレン(PP)+PE)、酸素供給系(ポリカーボネート+PPの中空膜)。

それらすべての構成成分を三工程処理により表面-ヘパリン化した：

- 1) 過硫酸アンモニウム(1%, 60℃, 120分間)
- 2) ポリエチレンジオキサン(0.3g/μl, 希硫酸緩衝液、pH 9、室温、15分間)
- 3) 実施例1に従って調整されたヘパリン-ポリリジン複合体を、

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また、それらを塩化ナトリウム溶液で洗浄した。次にそれらチューブをトロンビンの溶液と共にインキュベートし(15μl/μl, 10分間、室温、暗黒下)そして塩化ナトリウム溶液で洗浄した。次にそれらチューブの半分をフィブリノーゲン除去した装置と共に58秒間インキュベートした。貧血-結合トロンビン活性は、それらチューブをトロンビンの標準性基質と共に60秒間インキュベート後反応をクエン酸緩衝液により止めることにより測定した。得られる吸光度を405nmで測定した。次の結果が得られた。

	ヘパリンA との複合体	ヘパリンB(脱炭酸 化合物)との複合体
トロンビン検出 (フィブリノーゲン 除去法不使用)	0.639±0.090	0.611±0.156
トロンビン検出量 (フィブリノーゲン 除去法不使用)	0.038±0.001	0.046±0.001

この結果は、いずれの調整後もトロンビンの前記および阻害に關し完全に満足できる結果を与えることを示している。

実施例2

各置換度を有する複合体および表面結合生物学的活性試験
複合体1と称される複合体を実施例1の記載と同様にして調整した。ポリリジン1個あたりのヘパリンの置換度は240:1であった。

次に複合体2と称される別の複合体を調整した。この場合の出発材料は、SPDP基の前にポリリジン溶液中のpHを3に調整することにより調整された、より低いSPDP置換度のポリリジンであった。その置換度は1ポリリジン分子あたり633 SPDP基と測定された。

0.5M NaClを添加したクエン酸緩衝液、pH 3.8中、30mg/μlまで希釈し、そして室温で120分間培養した。前記構成成分を最後に、希硫酸緩衝液、pH 9および水で2×15分間洗浄した。乾燥後、エチレンジオキサンによる処理を行った。

この体外システムを右心室と大動脈の間の部分バイパスに対し抗血栓形成法を受けていない新鮮ブタに移植した。この体外システムは、24時間間隔にわたり連続的に約8μl/分をポンプ輸送したが凝固による血栓の問題は全くなかった。凝固問題は常に一定値であったが、このことは血液凝結へのヘパリン遊離はなかったことを示している。

これらの結果は、体外リポート装置用の完全システムをヘパリン複合体で表面-ヘパリン化することにより、エチレンジオキサンで滅菌できる、安定で十分機能するヘパリン表面を得ることができることを実証している。

実施例4

血液中の各種ヘパリン-複合体の生物学的活性の試験

様々な置換度を行なうヘパリン-ポリリジン複合体を実施例1および2に従って調整した。複合体の生物学的活性を、抗トロンビン活性緩衝液または血液凝結中における第3a因子およびトロンビン阻害剤について測定した。得られた結果を既知の生物学的活性(186 I.U./μg)を有する低置換度のヘパリンを添加することにより得られる対応グラフと比較した。次の結果が得られた。

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試料	ヘパリン/ ポリリジン	Is/AT	Is/AT	Tr/AT	Tr/AT
I	235	116	95	48	45
II	190	51	29	10	20
III	658	10	43	18	25

それらの結果は、試験のプロセスが低い生物学的活性および低い生物学的活性を有する複合体の調製に用いることができることを示している。

表 1

様々なポリリジンのサイズの効果

それぞれ13,000、64,000、98,000、249,000および464,000の分子量を有する異なるサイズのポリリジンを実施例1に従ってSPDPで変性して、次の置換度（ポリリジン1分子あたりSPDP-基数）が得られた。

試料	分子量	置換度
I	13,000	6
II	64,000	21
III	98,000	45
IV	249,000	35
V	249,000	87
VI	464,000	158

第一級アミンのための標準的目盛りで1,000の量を有するヘパリンを実施例1に従って、蔗糖チオール基を導入するためにSPDPで変性して、0.2~0.3の置換度を得た。それぞれの複合体は実施例1に従って調製した。分離は、Sepharyl® S-500またはSephacryl® S-

M NoC4で抽出した。空腔分を求め、そしてSPDPの反応について分析した。SPDPの含量は、キトサン1分子あたり約10 SPDP基に相当する0.972μmol/μlと測定された。

蔗糖チオール基を有するヘパリンを実施例1に従って調製した。得られたヘパリン溶液に次に糖化ナトリウムを2.5Mの最終濃度となるように添加した。次にそのヘパリン溶液を最終に調製したキトサン-SPDP複合体と混合して攪拌しながら添加し、そして反応を室温で一晩進行させた。反応完了後、反応が100%まで進行したことを示していた。その結果をSephacryl® S-500(Pharmacia LKB Biotechnology AB社、スウェーデン)で分離し、そして空腔分を求めた。Pelax® (Ateche社、フランス)のポリエチレンブロッグアミド)のチューブを実施例1によるトロンビン試験のために調製した。次の結果が得られた：

トロンビン阻害 (フィブリノーゲン 除去法で測定)	トロンビン阻害 (フィブリノーゲン 除去法で測定)
0.491±0.016	0.002

これらの結果は、キトサン-ヘパリン複合体を用いて調製された表面が完全に凝固できる結果を与えることを実証している。

表 2

ポリリジンとヘパリンの複合体の調製

10mgのポリリジン（Aldrich社、分子量約50,000）を1.5mlの水溶液に溶解し、それに1.0mlのSPDP（10mg/ml）を添加しながら攪拌し、そして30分間反応させた。その溶液をPD-10カラムにかけ、それを0.9%NaClで抽出した。空腔分を求め、そして分析したところポリリジン1分子あたり約102

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408(Pharmacia LKB Biotechnology AB社、スウェーデン)を分離体とするカラムで抽出した。複合体1は蔗糖ヘパリンから分離し得なかった。他の複合体については、満足できる分離が得られ、また得られた複合体は、実施例1に従ってチューブを蔗糖-ヘパリン化するために用いることができる。（実施例1に従った）トロンビンの凝固および阻害に関する試験は次の結果を与えた：

試料	トロンビン阻害 (フィブリノーゲン 除去法で測定)	トロンビン阻害 (フィブリノーゲン 除去法で測定)
I	---	---
II	0.012±0.006	0
III	0.086±0.047	0
IV	0.494±0.009	0.003
V	0.532±0.043	0.000
VI	0.480±0.004	0.004

これらの結果は、複合体II-VIが本発明に従ってヘパリン活性を有する表面の調製に使用できることを示している。しかしながら複合体IV-VIが最高の結果を与えた。

表 4

キトサンを基体物質とする複合体の調製

キトサン (SesCure 116 L、粘度<20cP、分子量約120,000、Protein Biopolymer A/3社、ドラメン(Drammen)、ノルウェー)を、1%酢酸溶液に10mg/mlとなるよう溶解した。1.5mlの溶液に1.0mlのSPDP（10mg/ml）を60℃で置換しながら添加し、そして反応を1時間進行させた。試料をPD-10カラム（Pharmacia LKB Biotechnology AB社、スウェーデン）にかけ、そして1%酢酸溶液9.5

SPDP基に相当する0.16μmol/mlのSPDPを含むことが示された。この生成物を以下において複合体1の調製に用いた。

別の10mgのポリリジン（Aldrich社）を2.5Mの蔗糖チオール基に溶解し、前記と同様にSPDPで変性した。その場合、空腔分は、ポリリジン1分子あたり2.2 SPDP基に相当する1.56μmol SPDP/mlを含むことが示された。次いで、この生成物を以下の複合体1の調製に用いた。

もう一つの調製例では、pHを3.5に調整した1mlの水に溶解した2μmolのポリリジン（Aldrich社）を16μmolのシアノヒドリンの存在下に36μmolのホルムアルデヒドと反応させることにより部分的にメチル化してあるポリリジン（Aldrich社）を1.56μmol SPDP/mlを含むことが示された。次いで、この生成物を以下の複合体1の調製に用いた。

10mgの蔗糖チオール基を有するヘパリン（Aldrich社）を1.5mlの水溶液に溶解し、それに1.0mlのSPDP（10mg/ml）を添加しながら攪拌し、そして30分間反応させた。その溶液をPD-10カラムにかけ、それを0.9%NaClで抽出した。空腔分を求め、そして分析したところポリリジン1分子あたり約102

蔗糖チオール基を有するヘパリン（Aldrich社）を1.5mlの水溶液に溶解し、それに1.0mlのSPDP（10mg/ml）を添加しながら攪拌し、そして30分間反応させた。その溶液をPD-10カラムにかけ、それを0.9%NaClで抽出した。空腔分を求め、そして分析したところポリリジン1分子あたり約102

体Ⅰ、複合体Ⅱおよび複合体ⅢをそれぞれSepharcl 6B S-400カラム (Pharmacia LKB Biotechnology AB社、スウェーデン) で精製したところ、複合体は空欄成分中に含まれた。

得られた三種類のヘパリン複合体を用いて、実施例1によるトロンビン試験のためにポリエチレンチューブを調製し、次の結果を得た。

	トロンビン抑制 (フィブリノーゲン 凝固時間不反応)	トロンビン凝固量 (フィブリノーゲン 凝固時間不反応)
複合体Ⅰ	0.457±0.008	0.007±0.002
複合体Ⅱ	0.445±0.020	0.003±0.001
複合体Ⅲ	0.501±0.032	0.005±0.002

これらの結果は、三種類の複合体のすべてが完全に満足できる効果を与えることを実証している。

実施例8

様々なアミノ酸性質の表面を有する表面の調製

ポリエチレンチューブを次のようにしてヘパリン化した(付された図A、B、CおよびDはそれぞれチューブ表面の別の選択性としてのアミノ酸性質化処理を示している)：

1. 過硫酸アンモニウム (1%, 60°C, 60分間)
- 2A. ポリニチレンイミン (0.5mg/ml, ホレートpH9, 室温, 15分間)
- 2B. ポリアリルアミン (10mg/ml, ホレートpH9, 室温, 15分間)
- 2C. ナトリウム (10mg/ml, 1% NaCl, 室温, 15分間)
- 2D. ポリリジン (水中5mg/ml, 室温, 15分間)
3. 実施例1に従って調製されたヘパリン-ポリリジン複合体(ク

して塩化ナトリウム溶液で十分洗浄した。ここで得られたチューブを様々な活性成分の血小板および血漿タンパク質より成る血漿成分で処理した。実施例1に従って調製されたヘパリン-ポリリジン複合体を塩化ナトリウム溶液中で10mg/mlの最終濃度となるように希釈し、次にその溶液をそれらチューブ内で60分間回転させた。それらチューブを最後に、水中で十分洗浄し、pH9および水で十分洗浄した。

このようにしてヘパリン化されたチューブを実施例1に従ってトロンビンの凝固および阻害について試験したところ、各チューブは完全に満足できる結果を示した。

実施例9

ウレアーゼとの組合せ調製

ポリリジン (10mg, 分子量61,000) を1.5mgの水に溶解し、それに1.0mgのSPBP (10mg/ml NaOH) を投与しながら溶解し、次に反応を30分間進行させた。その試料をPD-10カラムにかけ、そして0.9% NaClで洗脱した。空欄成分を集め、そして分析したところSPBP含量が1.053mg/mlであることが示された。

ウレアーゼ (4-1500, クロマトマノ由、Sigma社、米国) をリン酸緩衝液、pH7.5に10mg/mlとなるように溶解し、そして0.22mg/mlを添加して反応させた。過剰反応含量は0.131mg/mlと測定された。

3 M NaClに溶解したポリリジン-SPBPをウレアーゼと、利用可能なSPBP量の約10%がウレアーゼのSQ基とのジスルフィド交換を受け得るように混合した。342nmにおける分光光度測定によりこれが実証されたことが確認された。次に実施例1に従って過剰SPBP

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エン酸緩衝液中50mg/ml, 0.04 M NaCl, pH7.5, 室温, 120分間)

このようにして調製された表面をポリエチレンチューブで十分洗浄した。

前述の四つの選択性に従ってヘパリン化されたポリエチレンチューブを実施例1に記載された如く、トロンビンの凝固および阻害について試験したところ、すべての選択性が完全に満足できる結果を示した。

実施例10

レンズ(PH)の表面-ヘパリン化および血小板付着試験

ポリメチルメタクリレート (PMMA) の既成レンズを実施例1に従ってヘパリン化した後、血小板付着について試験した。

無菌性レンズおよび表面-ヘパリン化レンズをそれぞれ、新鮮ヒトクエン酸リン酸塩溶液中で一晩の静置を与えながら60分間インキュベートした。それらレンズを次に塩化ナトリウム溶液中でくり返し洗浄してすべての付着成分を除去した。最後にアデノシン三リン酸(ATP)をレンズ表面に付着したすべての血小板から抽出し、そして得られたATPの量をバイオルミネセンスにより測定した。ヘパリン化レンズへの血小板付着は未処理レンズに比べ98%低下した。

実施例11

"生物学的表面"へのヘパリン複合体の吸着

本発明により調製されたヘパリン複合体が臨床応用生物学的材料で被覆された表面に不可逆的に吸着されるかどうかを調べるために次の実験を行った：

ポリエチレンの表面にヘパリン複合体をクエン酸リン酸塩溶液中で60分間回転させた。次にそれらチューブから血液を試しそ

で定性されたヘパリンを抽出した(ヘパリン-38mg/mlは利用可能なSPBP量の約80%に相当するものとした)。反応は完了するまで進行した。得られた複合体を最後にSepharcl 6B S-400カラム (Pharmacia LKB Biotechnology AB社、スウェーデン) で精製したところ、複合体は空欄成分中に含まれた。得られた複合体を試験したところヘパリン活性およびレアーゼ活性が抽出されることが示された。

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特許庁長官 宛

1. 図解出願の表示

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2. 発明の名称

新規複合体、その調製および使用ならびにその複合体を
用いて調製された基体

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特許書の組数又(請求の範囲)

1 通

7. 備考

請求項1および4が修正された。

8. 少なくとも100グリコサミノグリカン残基を有する請求項7記載の複合体。
9. 前記グリコサミノグリカンがヘパリンまたはその断片または誘導体である請求項1〜8のいずれか1項記載の複合体。
10. グリコサミノグリカン残基が複合配列を介してポリマー主鎖に結合される請求項1〜8のいずれか1項記載の複合体。
11. 前記複合配列がヘテロ-二官能性複合配列に由来する請求項10記載の複合体。
12. ポリマー主鎖がグリコサミノグリカン類のほかに少なくとも一つの付加的な生物学的に活性な残基を有する請求項1〜11のいずれか1項記載の複合体。
13. 複合体が多数の官能基をポリマー主鎖に沿って分布させた実質的に無数の有機ポリマーであって、それら官能基を介して糖酸化グリコサミノグリカン類からの多数の分子が共有結合を通して結合されているものより成り、該複合体は好ましくは該複合体と基体表面との間の静電的相互作用により表面に結合されていることを特徴とする。表面にアフィニティー結合された生物学的に活性な複合体より成る調製された基体表面。
14. 生物学的に活性な複合体が請求項1〜11のいずれか1項記載の複合体である請求項13記載の調製された基体表面。
15. 多数の官能基をポリマー主鎖に沿って分布させた実質的に無数の有機ポリマーを準備し、そしてこれら官能基に、所望によりは台座を介して、その非活性部分の糖酸化グリコサミノグリカン類からの多数の分子を共有結合的に結合させることより成ることを特徴とする。糖酸化グリコサミノグリカン類からの多数の分

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発 明 の 説 明

1. 多数の官能基をポリマー主鎖に沿って分布させた実質的に無数の有機ポリマーであって、それら官能基を介して糖酸化グリコサミノグリカン類からの少なくとも約20分子が共有結合を通して結合され、そしてグリコサミノグリカンが該グリコサミノグリカンの非活性部分において実質的に無結合を介してポリマー主鎖に結合されているものより成る実質的に永続的な生物学的に活性な複合体。
2. 前記ポリマーが突然または合成のポリペプチド、多糖体または脂肪族ポリマーに由来する請求項1記載の複合体。
3. 前記ポリマーがポリリジン、ポリオルニチン、ホトリン、ポリイミンまたはポリアルギニンに由来する請求項2記載の複合体。
4. グリコサミノグリカン類が実質的にポリマー主鎖に結合されている請求項1、2または3のいずれか1項記載の複合体。
5. グリコサミノグリカン類が該グリコサミノグリカン類に結合したアミノ基を介したポリマー主鎖に結合されている請求項1〜4のいずれか1項記載の複合体。
6. 複合体がそのグリコサミノグリカン類のほかに、水に溶解された場合に実質的にその全長に沿って正電荷基に静電的相互作用により実質的に不可逆的に結合され得るのに十分なポリ陰イオン特性を有することをも特徴とする請求項1〜5のいずれか1項記載の複合体。
7. 少なくとも30グリコサミノグリカン残基を有する請求項1〜6のいずれか1項記載の複合体。
8. 多数の官能基をポリマー主鎖に沿って分布させた実質的に無数の有機ポリマーであって、それら官能基を介して糖酸化グリコサミノグリカン類からの多数の分子が共有結合を通して結合されているものより成る複合体を該複合体に対するアフィニティーを有する基体表面と、複合体がそこに実質的に不可逆的に結合されるように接触させることを特徴とする。糖酸化グリコサミノグリカン類による表面の調製方法。
9. 複合体がポリ陰イオン特性を有し、基体表面が陽イオン性である請求項16記載の方法。
10. 治療剤として用いるための請求項1〜12のいずれか1項記載の生物学的に活性な複合体。

子を維持する実質的に無数の有機ポリマーより成る生物学的に活性な複合体の調製方法。

特表平6-510783 (11)

国際特許条約

国際特許条約

PCT/SE 92/06672

1. CLASSIFICATION OF THE INVENTION IN ACCORDANCE WITH THE INTERNATIONAL PATENT CLASSIFICATION (IPC) CLASS

IPC: A 61 K 31/27, 42/42, A 61 L 31/00, C 60 B 37/10

2. PRIOR ART

3. SUMMARY OF THE INVENTION

4. BRIEF DESCRIPTION OF THE DRAWINGS

5. DETAILED DESCRIPTION OF THE INVENTION

6. CLAIMS

7. REFERENCES

8. OTHER INFORMATION

9. ABSTRACT

10. PUBLICATION INFORMATION

11. PUBLICATION INFORMATION

12. PUBLICATION INFORMATION

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		EP-A-	680754	89-06-30
		EP-A-	6228387	87-07-16
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		JP-A-	4937181	91-01-12
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4. 補正命令の内容(自己)

5. 補正対象範囲

明細書、請求の範囲

6. 補正対象項目

明細書、請求の範囲

7. 補正の内容

1) 請求の範囲を訂正のとおり補正します。

2) 明細書第2項第14行の「花びら状の部」を「花びら状の部」と修正します。

3) 図第7頁下から6行の「そのa」を「そのb」と修正します。

4) 図第12頁上から5行の「図10」を「図11」と修正します。

以上

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